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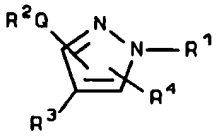
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(54) Title: PYRAZOLE DERIVATIVES AS p38 KINASE INHIBITORS

(57) Abstract

A class of pyrazole derivatives is described for use in treating p38 kinase mediated disorders. Compounds of particular interest are defined by Formula (I) wherein Q, R_1, R_2, R_3 and R_4 are as described in the specification.



(I)

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PYRAZOLE DERIVATIVES AS p38 KINASE INHIBITORS

Cross-Reference to Related Application

This application claims priority from U.S. Provisional Application Serial No. 60/047,569 filed May 22, 1997.

Field of the Invention

This invention relates to a novel group of pyrazole compounds, compositions and methods for treating p38 kinase mediated disorders.

Background of the Invention

Mitogen-activated protein kinases (MAP) is a family of proline-directed serine/threonine kinases that activate their substrates by dual phosphorylation. The kinases are activated by a variety of signals including nutritional and osmotic stress, UV light, growth factors, endotoxin and inflammatory cytokines. The p38 MAP kinase group is a MAP family of various isoforms, including p38α, p38β and p38γ, and is responsible for phosphorylating and activating transcription factors (e.g. ATF2, CHOP and MEF2C) as well as other kinases (e.g. MAPKAP-2 and MAPKAP-3). The p38 isoforms are activated by bacterial lipopolysaccharide, physical and chemical stress and by pro-inflammatory cytokines, including tumor necrosis factor (TNF-α) and interleukin-1 (IL-1). The products of the p38 phosphorylation mediate the production of inflammatory cytokines, including TNF and IL-1, and cyclooxygenase-2.

TNF-α is a cytokine produced primarily by activated monocytes and macrophages. Excessive or unregulated TNF production has been implicated in mediating a number of diseases. Recent studies indicate that TNF has a causative role in the pathogenesis of rheumatoid arthritis. Additional studies demonstrate that

inhibition of TNF has broad application in the treatment of inflammation, inflammatory bowel disease, multiple sclerosis and asthma.

TNF has also been implicated in viral infections, such as HIV, influenza virus, and herpes virus including herpes simplex virus type-1 (HSV-1), herpes simplex virus type-2 (HSV-2), cytomegalovirus (CMV), varicella-zoster virus (VZV), Epstein-Barr virus, human herpesvirus-6 (HHV-6), human herpesvirus-7 (HHV-7), human herpesvirus-8 (HHV-8), pseudorabies and rhinotracheitis, among others.

IL-8 is another pro-inflammatory cytokine, which is produced by mononuclear cells, fibroblasts, endothelial cells, and keratinocytes, and is associated with conditions including inflammation.

IL-1 is produced by activated monocytes and macrophages and is involved in the inflammatory response. IL-1 plays a role in many pathophysiological responses including rheumatoid arthritis, fever and reduction of bone resorption.

TNF, IL-1 and IL-8 affect a wide variety of cells and tissues and are important inflammatory mediators of a wide variety of disease states and conditions. The inhibition of these cytokines by inhibition of the p38 kinase is of benefit in controlling, reducing and alleviating many of these disease states.

Various pyrazoles have previously been described. U.S. Patent No. 4,000,281, to Beiler and Binon, describes 4,5-aryl/heteroaryl substituted pyrazoles with antiviral activity against both RNA and DNA viruses such as myxoviruses, adenoviruses, rhinoviruses, and various viruses of the herpes group. WO 92/19615, published November 12, 1992, describes pyrazoles as novel fungicides. U.S. Patent No. 3,984,431, to Cueremy and Renault, describes derivatives of pyrazole-5-acetic acid as having anti-inflammatory activity. Specifically, [1-isobutyl-3,4-diphenyl-1H-pyrazol-5-yl]acetic acid is

described. U. S. Patent No. 3,245,093 to Hinsgen et al, describes a process for preparing pyrazoles. WO 83/00330, published February 3, 1983, describes a new process for the preparation of diphenyl-3,4-methyl-5-pyrazole derivatives. WO 95/06036, published March 2, 1995, describes a process for preparing pyrazole derivatives. U.S. patent 5,589,439, to T. Goto, et al., describes tetrazole derivatives and their use as herbicides. EP 515041 describes pyrimidyl substituted pyrazole derivatives as novel agricultural fungicides. Japanese Patent 4,145,081 describes pyrazolecarboxylic acid derivatives as herbicides. Japanese Patent 5,345,772 describes novel pyrazole derivatives as inhibiting acetylcholinesterase.

Pyrazoles have been described for use in the treatment of inflammation. Japanese Patent 5,017,470 describes synthesis of pyrazole derivatives as anti-inflammatory, anti-rheumatic, anti-bacterial and anti-viral drugs. EP 115640, published December 30, 1983, describes 4-imidazolyl-pyrazole derivatives as inhibitors of thromboxane synthesis. 3-(4-Isopropyl-1-methylcyclohex-1-yl)-4-(imidazol-1-yl)-1H-pyrazole is specifically described. WO 97/01551, published January 16, 1997, describes pyrazole compounds as adenosine antagonists. 4-(3-Oxo-2,3-dihydropyridazin-6-yl)-3-phenylpyrazole is specifically described. U.S. Patent No. 5,134,142, to Matsuo et al. describes 1,5-diaryl pyrazoles as having anti-inflammatory activity.

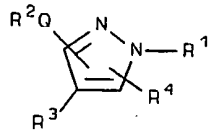
U.S. Patent No. 5,559,137 to Adams et al, describes novel pyrazoles (1,3,4,-substituted) as inhibitors of cytokines used in the treatment of cytokine diseases. Specifically, 3-(4-fluorophenyl)-1-(4-methylsulfinylphenyl)-4-(4-pyridyl)-5H-pyrazole is described. WO 96/03385, published February 8, 1996, describes 3,4-substituted pyrazoles, as having anti-inflammatory activity. Specifically, 4-[1-ethyl-4-(4-

pyridyl)-5-trifluoromethyl-1H-pyrazol-3-yl]benzenesulfonamide is described.

The invention's pyrazolyl compounds are found to show usefulness as p38 kinase inhibitors.

Description of the Invention

A class of substituted pyrazolyl compounds useful in treating p38 mediated disorders is defined by Formula I:

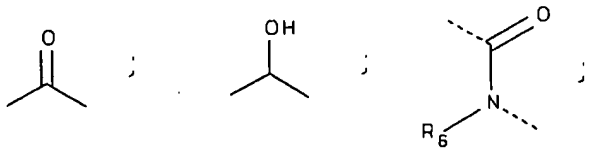


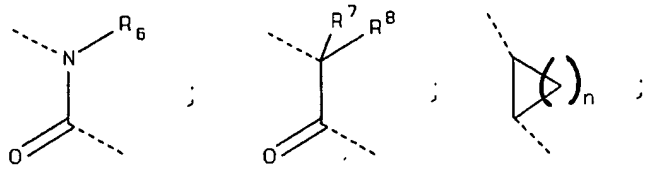
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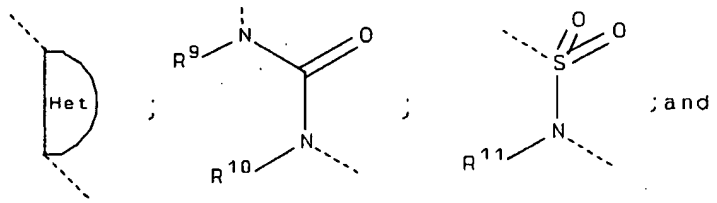
wherein

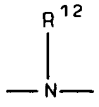
R^1 is selected from hydrido, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heterocyclyl, cycloalkylalkylene, cycloalkenylalkylene, haloalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, aralkyl, aralkenyl, aralkynyl, heterocyclylalkylene, alkoxyalkyl, aryloxyalkyl, heterocyclyloxyalkyl, mercaptoalkyl, mercaptoaryl, mercaptoheterocyclyl, alkylthioalkylene, arylthioalkylene, amino, alkylamino, arylamino, aminoalkyl, aminoaryl, alkylaminoalkylene, and heterocyclylalkylene; and

Q is selected from oxy, thio, alkylene, alkenylene, alkynylene, sulfinyl, sulfonyl,

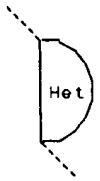








wherein



represents a four to eight membered ring heterocyclylidenyl comprising one or more heteroatoms selected from oxygen, sulfur and nitrogen; and

wherein n is an integer from 1 to 7; and

R^2 is aryl optionally substituted with one or more radicals independently selected from halo, alkyl, alkenyl, alkynyl, aryl, heterocyclyl, alkoxy, alkenoxy, alkynoxy, aryloxy, heterocyclyloxy, aralkoxy, alkylthio, arylthio, alkylsulfinyl, arylsulfinyl, alkylsulfonyl, arylsulfonyl, amino, alkylamino, alkenylamino,

alkynylamino, arylamino, heterocyclylamino, aminoalkyl, aminocarbonyl, cyano, hydroxyl, hydroxyalkyl, alkoxycarbonyl, aryloxycarbonyl, heterocyclyloxycarbonyl, formyl, nitro, nitroalkyl, alkylcarbonylamino, arylcarbonylamino, haloalkylsulfinyl, haloalkylsulfonyl, alkylcarbonyl, arylcarbonyl, heterocyclylcarbonyl, and haloalkyl; and

R^3 is heteroaryl optionally substituted with one or more radicals independently selected from halo, alkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, amino, aminocarbonyl, cyano, hydroxyl, alkoxycarbonyl, formyl, aralkyl, aralkyloxy, aralkylthio, aralkylamino, aminosulfonyl, alkylamino, nitro, arylamino, alkylcarbonylamino, halosulfonyl, aminoalkyl, haloalkyl and alkylcarbonyl; and

R^4 is selected from hydrido, alkyl, aryl, haloalkyl, heterocyclyl, cycloalkyl, alkenyl, cycloalkenyl, alkoxy, alkylthio, arylthio, carboxy, alkoxycarbonyl, carboxyalkyl, alkoxycarbonylalkylene, heterocyclylalkyl, amino, alkylamino, alkynylamino, arylamino, heterocyclylamino, heterocyclylalkylamino, heterocyclylaminoalkyl, and aminoheterocyclylamino; wherein the aryl, heterocyclyl, cycloalkyl, cycloalkenyl groups are optionally substituted with one or more radicals independently selected from halo, amino, alkyl, alkenyl, alkynyl, alkoxy, aryloxy, aralkoxy, haloalkyl, and alkylamino; and wherein the amino radicals of the heterocylcylalkylamino and heterocylcylaminoalkyl group are optionally substituted with one or more alkyl; and

R^6 is selected from hydrido, alkyl, alkenyl, and alkynyl; and

R^7 and R^8 are independently selected from hydrido, alkyl, alkenyl, and alkynyl, or together form a carbocyclic or heterocyclic ring having three to eight members; and

R^9 is selected from hydrido, alkyl, alkenyl, and alkynyl; and

R^{10} is selected from hydrido, alkyl, alkenyl, and alkynyl; and

R^{11} is selected from hydrido, alkyl, alkenyl, and alkynyl; and

R^{12} is selected from hydrido and alkyl; or

a pharmaceutically-acceptable salt or tautomer thereof.

Compounds of Formula I would be useful for, but not limited to, the treatment of any disorder or disease state in a human, or other mammal, which is exacerbated or caused by excessive or unregulated TNF or p38 kinase production by such mammal. Accordingly, the present invention provides a method of treating a cytokine-mediated disease which comprises administering an effective cytokine-interfering amount of a compound of Formula I, or a pharmaceutically acceptable salt or tautomer thereof.

Compounds of Formula I would be useful for, but not limited to, the treatment of inflammation in a subject, and for use as antipyretics for the treatment of fever. Compounds of the invention would be useful to treat arthritis, including but not limited to, rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis, osteoarthritis, gouty arthritis and other arthritic conditions. Such compounds would be useful for the treatment of pulmonary disorders or lung inflammation, including adult respiratory distress syndrome, pulmonary sarcoidosis, asthma, silicosis, and chronic pulmonary inflammatory disease. The compounds are also useful for the treatment of viral and bacterial infections, including sepsis, septic shock, gram negative sepsis, malaria, meningitis, cachexia secondary to

infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), pneumonia, and herpesvirus. The compounds are also useful for the treatment of bone resorption diseases, such as osteoporosis, endotoxic shock, toxic shock syndrome, reperfusion injury, autoimmune disease including graft vs. host reaction and allograft rejections, cardiovascular diseases including atherosclerosis, thrombosis, congestive heart failure, and cardiac reperfusion injury, renal reperfusion injury, liver disease and nephritis, and myalgias due to infection. The compounds are also useful for the treatment of influenza, multiple sclerosis, cancer, diabetes, systemic lupus erthrematosis (SLE), skin-related conditions such as psoriasis, eczema, burns, dermatitis, keloid formation, and scar tissue formation. Compounds of the invention also would be useful to treat gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis. The compounds would also be useful in the treatment of ophthalmic diseases, such as retinitis, retinopathies, uveitis, ocular photophobia, and of acute injury to the eye tissue. Compounds of the invention also would be useful for treatment of angiogenesis, including neoplasia; metastasis; ophthalmological conditions such as corneal graft rejection, ocular neovascularization, retinal neovascularization including neovascularization following injury or infection, diabetic retinopathy, retrolental fibroplasia and neovascular glaucoma; ulcerative diseases such as gastric ulcer; pathological, but non-malignant, conditions such as hemaginomas, including invantile hemaginomas, angiofibroma of the nasopharynx and avascular necrosis of bone; diabetic nephropathy and cardiomyopathy; and disorders of the female reproductive system such as endometriosis. The compounds of the

invention may also be useful for preventing the production of cyclooxygenase-2.

Besides being useful for human treatment, these compounds are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. More preferred animals include horses, dogs, and cats.

The present compounds may also be used in co-therapies, partially or completely, in place of other conventional anti-inflammatories, such as together with steroids, cyclooxygenase-2 inhibitors, NSAIDs, DMARDS, immunosuppressive agents, 5-lipoxygenase inhibitors, LTB_4 antagonists and LTA_4 hydrolase inhibitors.

As used herein, the term "TNF mediated disorder" refers to any and all disorders and disease states in which TNF plays a role, either by control of TNF itself, or by TNF causing another monokine to be released, such as but not limited to IL-1, IL-6 or IL-8. A disease state in which, for instance, IL-1 is a major component, and whose production or action, is exacerbated or secreted in response to TNF, would therefore be considered a disorder mediated by TNF.

As used herein, the term "p38 mediated disorder" refers to any and all disorders and disease states in which p38 plays a role, either by control of p38 itself, or by p38 causing another factor to be released, such as but not limited to IL-1, IL-6 or IL-8. A disease state in which, for instance, IL-1 is a major component, and whose production or action, is exacerbated or secreted in response to p38, would therefore be considered a disorder mediated by p38.

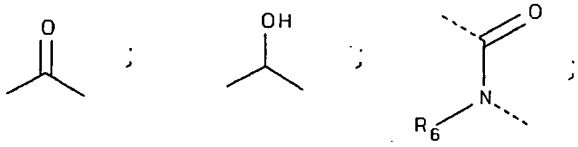
As TNF-β has close structural homology with TNF-α (also known as cachectin), and since each induces similar biologic responses and binds to the same cellular receptor, the synthesis of both TNF-α and TNF-β are inhibited by the compounds of the present invention and

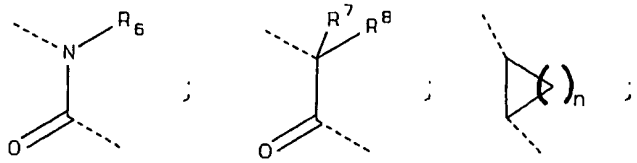
thus are herein referred to collectively as "TNF" unless specifically delineated otherwise.

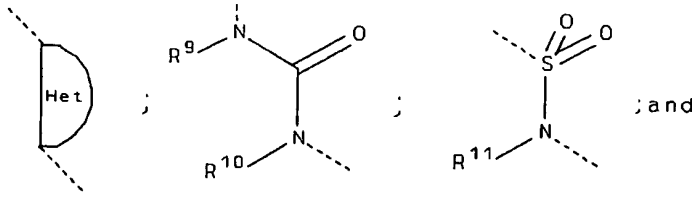
A preferred class of compounds consists of those compounds of Formula I wherein

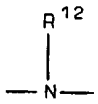
R^1 is selected from hydrido, lower alkyl, lower alkynyl, lower cycloalkylalkylene, lower haloalkyl, lower hydroxyalkyl, lower alkoxyalkyl, lower thioalkyl, lower alkylthioalkylene, amino, lower alkylamino, lower arylamino, lower alkylaminoalkylene, and lower heterocyclylalkylene; and

Q is selected from lower alkylene, lower alkenylene, sulfinyl, sulfonyl,









wherein



represents a four to eight membered ring heterocyclylidenyl comprising one or more heteroatoms selected from oxygen, sulfur and nitrogen; and

wherein n is an integer from 1 to 7; and

R^2 is aryl optionally substituted with one or more radicals independently selected from halo, lower alkyl, lower alkoxy, lower aryloxy, lower aralkoxy, amino, hydroxyl, nitro, cyano, lower haloalkyl, lower alkylamino, and lower alkynylamino; and

R^3 is selected from 5- to 10-membered heterocyclyl optionally substituted with one or more radicals independently selected from lower alkylthio, lower alkylsulfonyl, aminosulfonyl, halo, lower alkyl, lower alkylsulfinyl, cyano, lower alkoxycarbonyl, aminocarbonyl, formyl, lower aralkyl, lower aralkyloxy, lower aralkylthio, lower aralkylamino, lower alkylcarbonylamino, lower haloalkyl, hydroxyl, lower alkoxy, amino, lower alkylamino, lower aminoalkyl, phenylamino, nitro, halosulfonyl and lower alkylcarbonyl; and

R^4 is selected from hydrido, lower alkyl, aryl, lower haloalkyl, 5-10 membered heterocyclyl, lower alkylamino, lower alkynylamino, phenylamino, lower cycloalkyl, lower alkenyl, lower cycloalkenyl, lower alkoxy, lower alkylthio, carboxy, lower alkoxycarbonyl, lower carboxyalkyl, lower alkoxycarbonylalkylene, lower heterocyclylalkyl, lower heterocylcylalkylamino, and lower heterocylcylaminoalkyl; wherein the aryl, 5-10 membered heteroaryl, lower cycloalkyl and lower cycloalkenyl groups are optionally substituted with one or more radicals independently selected from halo, lower

alkyl, lower alkenyl, lower alkynyl, alkoxy, phenoxy, lower aralkoxy, lower haloalkyl, and lower alkylamino; and wherein the amino radicals of the lower heterocylcylalkylamino and lower heterocylcylaminoalkyl group are optionally substituted with one or more lower alkyl; and

R^6 is selected from hydrido, lower alkyl, lower alkenyl, and lower alkynyl; and

R^7 and R^8 are independently selected from hydrido, lower lower alkyl, lower alkenyl, and lower alkynyl, or together form a carbocyclic or heterocyclic ring having three to eight members; and

R^9 is selected from hydrido, lower alkyl, lower alkenyl, and lower alkynyl; and

R^{10} is selected from hydrido, lower alkyl, lower alkenyl, and lower alkynyl; and

R^{11} is selected from hydrido, lower alkyl, lower alkenyl, and lower alkynyl; and

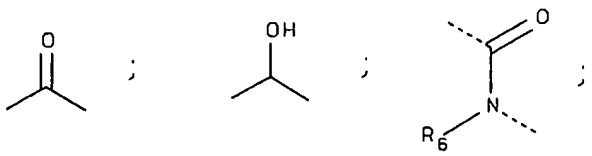
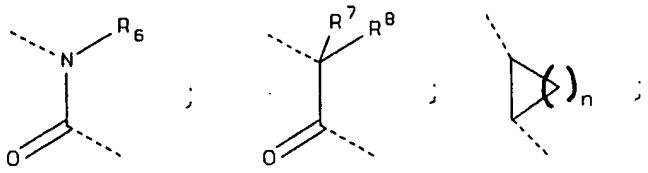
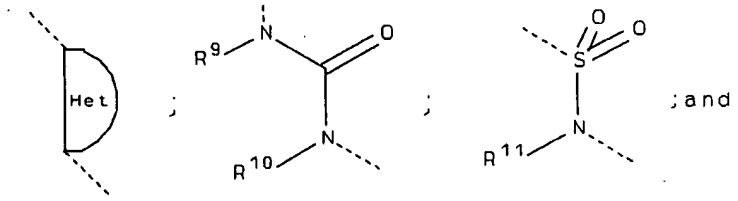
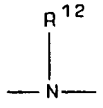
R^{12} is selected from hydrido and lower alkyl; or

a pharmaceutically-acceptable salt or tautomer thereof.

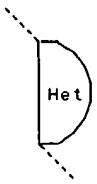
A more preferred class of compounds consists of those compounds of Formula I wherein

R^1 is selected from hydrido, lower alkyl, lower alkynyl, lower cycloalkylalkylene, lower haloalkyl, lower hydroxyalkyl, lower alkoxyalkyl, lower thioalkyl, lower alkylthioalkylene, lower alkylaminoalkylene, and lower heterocyclylalkylene; and

Q is selected from lower alkylene, lower alkenylene,

wherein



represents a four to eight membered ring heterocyclylidenyl comprising one or more heteroatoms selected from oxygen, sulfur and nitrogen; and

wherein n is an integer from 1 to 7; and

R^2 is aryl optionally substituted with one or more radicals independently selected from halo, lower alkyl, lower alkoxy, lower aryloxy, lower aralkoxy, amino, hydroxyl, nitro, cyano, lower haloalkyl, lower alkylamino, and lower alkynylamino; and

R^3 is 6-membered heteroaryl optionally substituted with one or more radicals independently selected from halo, lower alkyl, cyano, phenethyl, benzyl, benzyloxy, benzylthio, benzylamino, phenethylamino, aminocarbonyl, lower alkylcarbonylamino, hydroxyl, amino, lower alkylamino, lower aminoalkyl, and phenylamino; and

R^4 is selected from hydrido, lower alkyl, phenyl, lower haloalkyl, 5-10 membered heterocyclyl, lower alkylamino, lower alkynylamino, phenylamino, lower cycloalkyl, lower alkenyl, lower cycloalkenyl, lower alkoxy, lower heterocyclylaminoalkyl, and lower heterocyclylalkylamino; wherein the phenyl, 5-10 membered heteroaryl, lower cycloalkyl and lower cycloalkenyl groups are optionally substituted with one or more radicals independently selected from halo, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, phenoxy, lower aralkoxy, lower haloalkyl, amino, hydroxyl, cyano and lower alkylamino; and wherein the amino radicals of lower heterocyclyl alkylamino and lower heterocyclylaminoalkyl are optionally substituted with one or more lower alkyl; and

R^6 is selected from hydrido, lower alkyl, lower alkenyl, and lower alkynyl; and

R^7 and R^8 are independently selected from hydrido, lower lower alkyl, lower alkenyl, and lower alkynyl, or together form a carbocyclic or heterocyclic ring having three to eight members; and

R^9 is selected from hydrido, lower alkyl, lower alkenyl, and lower alkynyl; and

R^{10} is selected from hydrido, lower alkyl, lower alkenyl, and lower alkynyl; and

R^{11} is selected from hydrido, lower alkyl, lower alkenyl, and lower alkynyl; and

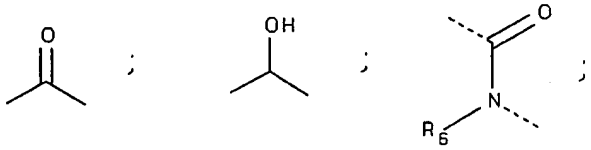
R^{12} is selected from hydrido and lower alkyl; or

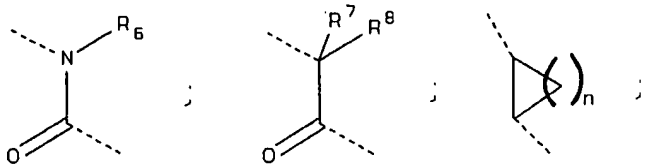
a pharmaceutically-acceptable salt or tautomer thereof.

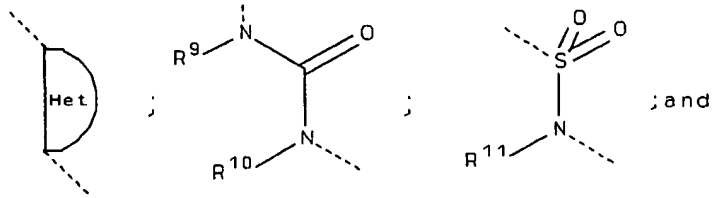
A class of compounds of particular interest consists of those compounds of Formula I wherein

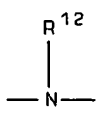
R^1 is selected from hydrido, methyl, ethyl, propyl, isopropyl, tert-butyl, isobutyl, ethynyl, propargyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloroethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, morpholinomethyl, pyrrolidinylmethyl, piperazinylmethyl, piperidinylmethyl, pyridylmethyl, thienylmethyl, methoxymethyl, ethoxymethyl, methylaminomethyl, cyclohexylmethyl, hydroxymethyl, hydroxylethyl, thiomethyl, and methylthiomethyl; and

Q is selected from methylene, ethylene, propylene, ethenylene, propenylenyl

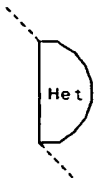








wherein



represents a four to eight membered ring heterocyclylidenyl comprising one or more heteroatoms selected from oxygen, sulfur and nitrogen; and

wherein n is an integer from 1 to 7; and

R^2 is phenyl optionally substituted with one or more radicals independently selected from fluoro, chloro, bromo, methyl, ethyl, isopropyl, tert-butyl, isobutyl, methoxy, ethoxy, phenoxy, benzyloxy, trifluoromethyl, fluoromethyl, difluoromethyl, amino, cyano, nitro, dimethylamino, ethynylamino, propargylamino, and hydroxyl; and

R^3 is selected from pyridyl, pyridium, and pyrimidyl; wherein R^3 is optionally substituted with one or more radicals independently selected from fluoro, chloro, bromo, methyl, ethyl, isopropyl, cyano, aminocarbonyl, methylcarbonylamino, hydroxy, benzyl, phenethyl, methylamino, ethylamino, dimethylamino, diethylamino, aminomethyl, aminoethyl, N-methyl-N-phenylamino, phenylamino, diphenylamino, benzylamino, phenethylamino, and amino; and

R^4 is selected from hydrido, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, isobutyl, phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, pyridyl, thienyl, isothiazolyl, isoxazolyl, thiazolyl, oxazolyl, pyrimidinyl, quinolyl, isoquinolinyl, imidazolyl, benzimidazolyl, furyl, benzofuryl, methoxy, ethoxy, trifluoromethyl, fluoromethyl, methylamino, ethynylamino, propargylamino, piperidinyl, piperazinyl,

piperadinylmethyl, piperadinylmethylamino, piperadinylaminomethyl, piperazinylmethyl, piperazinylmethylamino, piperazinylaminomethyl; wherein the phenyl piperadinyl and piperazinyl groups are optionally substituted with one or more radicals independently selected from fluoro, chloro, bromo, methyl, ethyl, isopropyl, tert-butyl, isobutyl, propargyl, methoxy, ethoxy, phenoxy, benzyloxy, trifluoromethyl, fluoromethyl, difluoromethyl, amino, hydroxyl, cyano and dimethylamino; and wherein the amino radicals of piperadinylmethylamino, piperadinylaminomethyl, piperazinylmethylamino, and piperazinylaminomethyl are optionally substituted with one or more methyl; and

R^6 is selected from hydrido, methyl, ethyl, propyl, isopropyl, tert-butyl, and isobutyl; and

R^7 and R^8 are independently selected from hydrido, methyl, ethyl, propyl, isopropyl, tert-butyl, and isobutyl, or together form a carbocyclic or heterocyclic ring having three to eight members; and

R^9 is selected from hydrido, methyl, ethyl, propyl, isopropyl, tert-butyl, and isobutyl; and

R^{10} is selected from hydrido, methyl, ethyl, propyl, isopropyl, tert-butyl, and isobutyl; and

R^{11} is selected from hydrido, methyl, ethyl, propyl, isopropyl, tert-butyl, and isobutyl; and

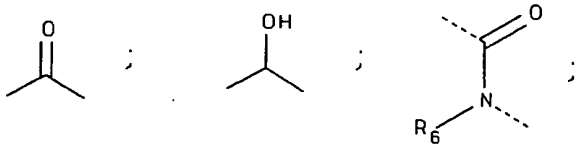
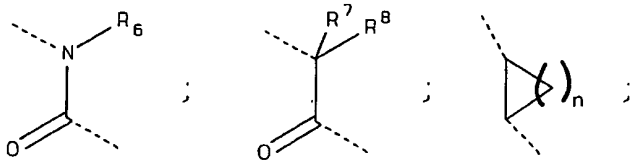
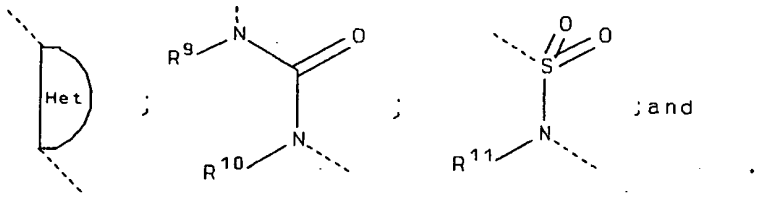
R^{12} is selected from hydrido, methyl, ethyl, propyl, isopropyl, tert-butyl, and isobutyl; or

a pharmaceutically-acceptable salt or tautomer thereof.

A class of compounds of specific interest consists of those compounds of Formula I wherein

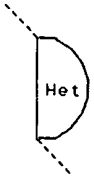
R^1 is hydrido or methyl; and

Q is selected from methylene, ethylene, ethenylene,



wherein



represents a four to eight membered ring heterocyclylidenyl comprising one or more heteroatoms selected from oxygen, sulfur and nitrogen; and

wherein n is an integer from 1 to 3; and

R^2 is phenyl optionally substituted with one or more radicals independently selected from fluoro, chloro, bromo, methyl, ethyl, isopropyl, tert-butyl, isobutyl, methoxy, ethoxy, phenoxy, benzyloxy, trifluoromethyl, fluoromethyl, difluoromethyl, amino, cyano, nitro, dimethylamino, and hydroxyl; and

R^3 is pyridyl optionally substituted with one or more radicals independently selected from fluoro, chloro, bromo, methyl, cyano, benzyl, phenethyl, aminocarbonyl, hydroxyl, dimethylamino, benzylamino, phenethylamino, aminomethyl and amino; and

R^4 is selected from hydrido, methyl, ethyl, propyl, propargylamino, and phenyl optionally substituted with one or more radicals independently selected from fluoro, chloro, bromo, methyl, ethyl, isopropyl, methoxy, ethoxy, phenoxy, benzyloxy, trifluoromethyl, dimethylamino, ethynylamino and propargylamino; and

R^6 is selected from hydrido and methyl; and

R^7 and R^8 are independently selected from hydrido and methyl; and

R^9 is selected from hydrido and methyl; and

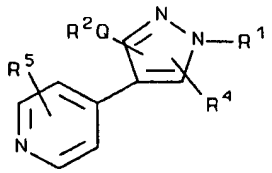
R^{10} is selected from hydrido and methyl; and

R^{11} is selected from hydrido and methyl; and

R^{12} is selected from hydrido and methyl; or

a pharmaceutically-acceptable salt or tautomer thereof.

Within Formula I there is a subclass of compounds of high interest represented by Formula II:

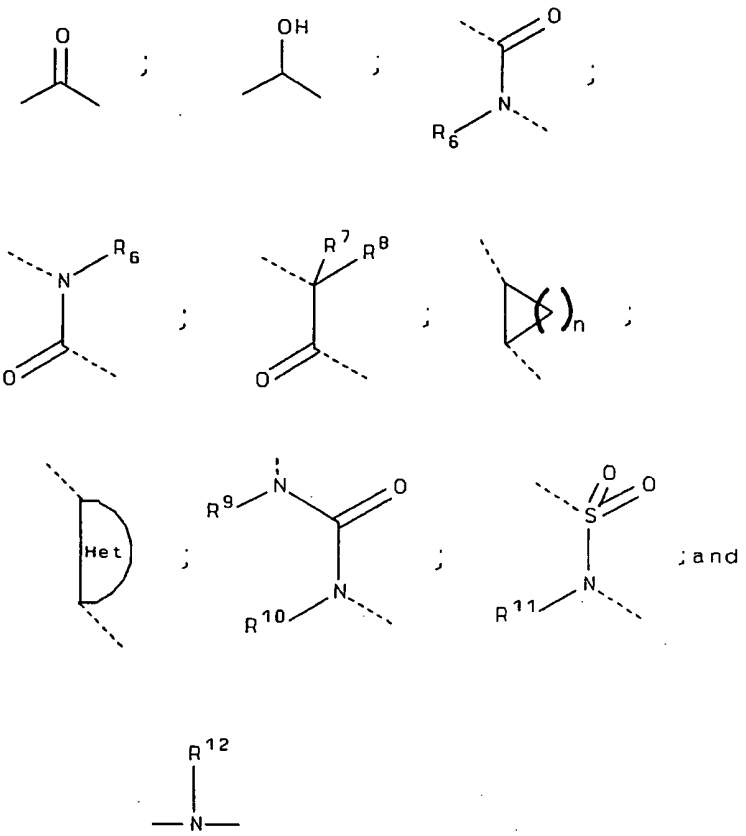


(II)

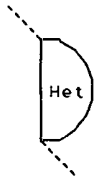
wherein

R^1 is selected from hydrido and lower alkyl; and

Q is selected from lower alkylene, lower alkenylene,



wherein



represents a four to eight membered ring heterocyclylidenyl comprising one or more heteroatoms selected from oxygen, sulfur and nitrogen; and

wherein n is an integer from 1 to 4; and

R^2 is phenyl optionally substituted with one or more radicals independently selected from halo and lower alkyl; and

R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are independently selected from hydrido and lower alkyl; or

a pharmaceutically-acceptable salt or tautomer thereof.

A preferred class of compounds consists of those compounds of Formula II wherein

R^1 is selected from hydrido and methyl; and

wherein Q is selected from methylene, ethylene, ethenylene,  and ;

R^2 is phenyl optionally substituted with one or more radicals independently selected from fluoro, chloro and bromo; and

R^4 is selected from hydrido, methyl and ethyl; and

R^5 is selected from hydrido and methyl; or

a pharmaceutically-acceptable salt or tautomer thereof.

A family of specific compounds of particular interest within Formula I consists of compounds, tautomers and pharmaceutically-acceptable salts thereof as follows:

4-[3-methyl-5-(2-phenylethenyl)-1H-pyrazol-4-yl]pyridine;

4-[3-methyl-5-(2-phenylethyl)-1H-pyrazol-4-yl]pyridine;

4-[3-methyl-5-[2-(3-fluorophenyl)ethyl]-1H-pyrazol-4-yl]pyridine;

4-[3-[2-(3-fluorophenyl)ethyl]-1H-pyrazol-4-yl]pyridine;

4-[1-methyl-3-[2-(3-fluorophenyl)ethyl]-1H-pyrazol-4-yl]pyridine;

4-[3-[2-(4-chlorophenyl)ethyl]-1H-pyrazol-4-yl]pyridine;

4-[1-methyl-3-[2-(4-chlorophenyl)ethyl]-1H-pyrazol-4-yl]pyridine;

3-methyl-4-[1-methyl-3-[2-(4-chlorophenyl)ethyl]-1H-pyrazol-4-yl]pyridine;

4-[3-[2-(3-chlorophenyl)ethyl]-1H-pyrazol-4-yl]pyridine;

3-methyl-4-[1-methyl-3-[2-(3,4-dichlorophenyl)ethyl]-1H-pyrazol-4-yl]pyridine;
3-methyl-4-[1-methyl-3-[2-(4-chlorophenyl)ethyl]-1H-pyrazol-4-yl]pyridine;
4-[3-methyl-5-[2-(3-fluorophenyl)ethenyl]-1H-pyrazol-4-yl]pyridine;
4-[3-[2-(3-fluorophenyl)ethenyl]-1H-pyrazol-4-yl]pyridine;
4-[1-methyl-3-[2-(3-fluorophenyl)ethenyl]-1H-pyrazol-4-yl]pyridine;
4-[3-[2-(4-chlorophenyl)ethenyl]-1H-pyrazol-4-yl]pyridine;
4-[1-methyl-3-[2-(4-chlorophenyl)ethenyl]-1H-pyrazol-4-yl]pyridine;
3-methyl-4-[1-methyl-3-[2-(4-chlorophenyl)ethenyl]-1H-pyrazol-4-yl]pyridine;
4-[3-[2-(3-chlorophenyl)ethenyl]-1H-pyrazol-4-yl]pyridine;
3-methyl-4-[1-methyl-3-[2-(3,4-dichlorophenyl)ethenyl]-1H-pyrazol-4-yl]pyridine;
3-methyl-4-[1-methyl-3-[2-(4-chlorophenyl)ethenyl]-1H-pyrazol-4-yl]pyridine;
4-[3-methyl-5-(3-fluorobenzyl)-1H-pyrazol-4-yl]pyridine;
4-[3-(3-fluorobenzyl)-1H-pyrazol-4-yl]pyridine;
4-[1-methyl-3-(3-fluorobenzyl)-1H-pyrazol-4-yl]pyridine;
4-[3-benzyl-1H-pyrazol-4-yl]pyridine;
4-[3-(4-chlorobenzyl)-1H-pyrazol-4-yl]pyridine;
4-[1-methyl-3-(4-chlorobenzyl)-1H-pyrazol-4-yl]pyridine;
3-methyl-4-[1-methyl-3-(4-chlorobenzyl)-1H-pyrazol-4-yl]pyridine;
4-[3-(3-chlorobenzyl)-1H-pyrazol-4-yl]pyridine;
3-methyl-4-[1-methyl-3-(3,4-dichlorobenzyl)-1H-pyrazol-4-yl]pyridine;
3-methyl-4-[1-methyl-3-(4-chlorobenzyl)-1H-pyrazol-4-yl]pyridine;

(3-fluorophenyl)[3-methyl-4-(4-pyridinyl)-1H-pyrazol-5-yl]methanone;
(3-fluorophenyl)[4-(4-pyridinyl)-1H-pyrazol-3-yl]methanone;
(3-fluorophenyl)[1-methyl-4-(4-pyridinyl)-1H-pyrazol-3-yl]methanone;
phenyl[1-methyl-4-(4-pyridinyl)-1H-pyrazol-3-yl]methanone;
(4-chlorophenyl)[4-(4-pyridinyl)-1H-pyrazol-3-yl]methanone;
(4-chlorophenyl)[1-methyl-4-(4-pyridinyl)-1H-pyrazol-3-yl]methanone;
(4-chlorophenyl)[1-methyl-4-(3-methyl-4-pyridinyl)-1H-pyrazol-3-yl]methanone;
(3-chlorophenyl)[4-(4-pyridinyl)-1H-pyrazol-3-yl]methanone;
(3,4-dichlorophenyl)[1-methyl-4-(3-methyl-4-pyridinyl)-1H-pyrazol-3-yl]methanone;
(4-chlorophenyl)[1-methyl-4-(3-methyl-4-pyridinyl)-1H-pyrazol-3-yl]methanone;
α-(3-fluorophenyl)-3-methyl-4-(4-pyridinyl)-1H-pyrazole-5-methanol;
α-(3-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazole-3-methanol;
α-(3-fluorophenyl)-1-methyl-4-(4-pyridinyl)-1H-pyrazole-3-methanol;
α-phenyl-1-methyl-4-(4-pyridinyl)-1H-pyrazole-3-methanol;
α-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazole-3-methanol;
α-(4-chlorophenyl)-1-methyl-4-(4-pyridinyl)-1H-pyrazole-3-methanol;
α-(4-chlorophenyl)-1-methyl-4-(3-methyl-4-pyridinyl)-1H-pyrazole-3-methanol;
α-(3-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazole-3-methanol;

α-(3,4-dichlorophenyl)-1-methyl-4-(3-methyl-4-pyridinyl)-1H-pyrazole-3-methanol;
α-(4-chlorophenyl)-1-methyl-4-(3-methyl-4-pyridinyl)-1H-pyrazole-3-methanol; and
4-[5-(2-phenylethyl)-1H-pyrazol-4-yl]pyridine.

The term "hydrido" denotes a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene (-CH_2-) radical. Where used, either alone or within other terms such as "haloalkyl", "alkylsulfonyl", "alkoxyalkyl" and "hydroxyalkyl", "mercaptoalkyl", the term "alkyl" embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, *tert*-butyl, pentyl, iso-amyl, hexyl and the like. The term "alkylene" embraces bridging alkyl radicals. The term "alkenyl" embraces linear or branched radicals having at least one carbon-carbon double bond of two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkenyl radicals are "lower alkenyl" radicals having two to about six carbon atoms. Examples of alkenyl radicals include ethenyl, 1-propenyl, allyl, 2-propenyl, butenyl and 4-methylbutenyl. The terms "alkenyl" and "lower alkenyl", embrace radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations. The term "alkenylene" describes bridging alkenyl radicals. The term "alkynyl" embraces linear or branched radicals having at least one carbon-carbon triple bond of two to about twenty carbon atoms

or, preferably, two to about twelve carbon atoms. More preferred alkynyl radicals are "lower alkynyl" radicals having two to about six carbon atoms. Examples of alkynyl radicals include ethynyl, propynyl and propargyl. The term "alkynylene" describes bridging alkynyl radicals. The term "cycloalkyl" embraces saturated carbocyclic radicals having three to about twelve carbon atoms. More preferred cycloalkyl radicals are "lower cycloalkyl" radicals having three to about eight carbon atoms. Examples of such radicals include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The term "cycloalkylalkylene" embraces alkyl radicals substituted with a cycloalkyl radical. More preferred cycloalkylalkylene radicals are "lower cycloalkylalkylene" which embrace lower alkyl radicals substituted with a lower cycloalkyl radical as defined above. Examples of such radicals include cyclopropylmethylene, cyclobutylmethylene, cyclopentylmethylene and cyclohexylmethylene. The term "cycloalkenyl" embraces partially unsaturated carbocyclic radicals having three to twelve carbon atoms. When a cycloalkenyl radical embraces partially unsaturated carbocyclic radicals which contain two double bonds but not necessary conjugated, it can be called "cycloalkyldienyl". More preferred cycloalkenyl radicals are "lower cycloalkenyl" radicals having four to about eight carbon atoms. Examples of such radicals include cyclobutenyl, cyclopentenyl and cyclohexenyl. The term "halo" means halogens such as fluorine, chlorine, bromine or iodine. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of

the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" embraces radicals having one to six carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms, any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl. The terms "alkoxy" and "alkyloxy" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and *tert*-butoxy. The term "alkoxyalkyl" embraces alkyl radicals having one or more alkoxy radicals attached to the alkyl radical to form, for example, monoalkoxyalkyl and dialkoxyalkyl radicals. The "alkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkoxy" radicals.

The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. More preferred aryl are 6-12 membered aryl. Examples of such radicals include, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl. Aryl moieties may also be substituted at a substitutable position with one or more

substituents selected independently from halo, alkyl, alkenyl, alkynyl, aryl, heterocyclyl, alkoxy, alkenoxy, alkynoxy, aryloxy, heterocyclyloxy, aralkoxy, alkylthio, arylthio, alkylsulfinyl, arylsulfinyl, alkylsulfonyl, arylsulfonyl, amino, alkylamino, alkenylamino, alkynylamino, arylamino, heterocyclylamino, aminoalkyl, aminocarbonyl, cyano, hydroxyl, hydroxyalkyl, alkoxycarbonyl, aryloxycarbonyl, heterocyclyloxycarbonyl, formyl, nitro, nitroalkyl, alkylcarbonylamino, arylcarbonylamino, haloalkylsulfinyl, haloalkylsulfonyl, alkylcarbonyl, arylcarbonyl, heterocyclylcarbonyl, haloalkyl, alkoxyalkyl, alkylaminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, acyl, carboxy, and aralkoxycarbonyl.

The term "heterocyclyl" embraces saturated, partially unsaturated and unsaturated heteroatom-containing ring-shaped radicals, which can also be called "heterocyclyl", "heterocycloalkenyl" and "heteroaryl" correspondingly, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Examples of saturated heterocyclyl radicals include saturated 3 to 6-membered heteromonocyclic group containing 1 to 4 nitrogen atoms (e.g. pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g. morpholinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., thiazolidinyl, etc.). Examples of partially unsaturated heterocyclyl radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole. Heterocyclyl radicals may include a pentavalent nitrogen, such as in tetrazolium and pyridinium radicals. The term "heteroaryl" embraces unsaturated heterocyclyl radicals. Examples of heteroaryl radicals include unsaturated 3 to 6 membered heteromonocyclic group containing 1 to 4

nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.) tetrazolyl (e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.; unsaturated condensed heterocyclyl group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl (e.g., tetrazolo[1,5-b]pyridazinyl, etc.), etc.; unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, furyl, etc.; unsaturated 3 to 6-membered heteromonocyclic group containing a sulfur atom, for example, thienyl, etc.; unsaturated 3- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.) etc.; unsaturated condensed heterocyclyl group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g. benzoxazolyl, benzoxadiazolyl, etc.); unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl (e.g., 1,2,4- thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.) etc.; unsaturated condensed heterocyclyl group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., benzothiazolyl, benzothiadiazolyl, etc.) and the like. The terms "heteroaryl and heterocyclyl" also embrace radicals where heterocyclyl radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. Said heterocyclyl group may have 1 to 3 substituents such as alkyl, hydroxyl, halo, alkoxy, oxo, amino and alkylamino. The term "heterocyclylalkylene" embraces saturated, partially unsaturated and unsaturated heterocyclyl-

substituted alkyl radicals. More preferred heterocyclylalkylene radicals are "lower heterocyclylalkylene" radicals having one to six carbon atoms and a heterocyclyl radical. Examples of such radicals include pyrrolidinylmethyl, pyridylmethyl, quinolylmethyl, thienylmethyl, furylethyl, and quinolylethyl. The heteroaryl group in said heteroaralkyl may be additionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy.

The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to about ten carbon atoms attached to a divalent sulfur atom. More preferred alkylthio radicals are "lower alkylthio" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthio radicals are methylthio, ethylthio, propylthio, butylthio and hexylthio. The term "alkylthioalkylene" embraces radicals containing an alkylthio radical attached through the divalent sulfur atom to an alkyl radical of one to about ten carbon atoms. More preferred alkylthioalkylene radicals are "lower alkylthioalkylene" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthioalkylene radicals include methylthiomethyl. The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to about ten carbon atoms, attached to a divalent -S(=O)- radical. More preferred alkylsulfinyl radicals are "lower alkylsulfinyl" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylsulfinyl radicals include methylsulfinyl, ethylsulfinyl, butylsulfinyl and hexylsulfinyl. The term "sulfonyl", whether used alone or linked to other terms, such as "alkylsulfonyl", or "halosulfonyl," denotes the divalent radical, $-SO_2-$. "Alkylsulfonyl" embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. More preferred alkylsulfonyl radicals

are "lower alkylsulfonyl" radicals having one to six carbon atoms. Examples of such lower alkylsulfonyl radicals include methylsulfonyl, ethylsulfonyl and propylsulfonyl. The "alkylsulfonyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkylsulfonyl radicals. The term "halosulfonyl" embraces halo radicals attached to a sulfonyl radical. Examples of such halosulfonyl radicals include chlorosulfonyl, and bromosulfonyl. The terms "sulfamyl", "aminosulfonyl" and "sulfonamidyl" denote NH_2O_2S-.

The term "carbonyl", whether used alone or with other terms, such as "alkoxycarbonyl", denotes . The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes $-CO_2H$. The term "carboxyalkyl" embraces alkyl radicals substituted with a carboxy radical. More preferred are "lower carboxyalkyl" radicals which embrace carboxy-substituted lower alkyl radicals as defined above. Examples of such lower carboxyalkyl radicals include carboxymethyl, carboxyethyl and carboxypropyl. The term "alkoxycarbonyl" means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl radical. More preferred are "lower alkoxycarbonyl" radicals with alkyl portions having one to six carbons. Examples of such lower alkoxycarbonyl (ester) radicals include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and hexyloxycarbonyl. The term "alkoxycarbonylalkylene" embraces alkylene radicals substituted with an alkoxycarbonyl radical as defined above. More preferred are "lower alkoxycarbonylalkylene" radicals with alkylene portions having one to six carbons. Examples of such lower alkoxycarbonylalkylene radicals include substituted or

unsubstituted methoxycarbonylmethyl, ethoxycarbonylmethyl, methoxycarbonylethyl and ethoxycarbonylethyl. The term "alkylcarbonyl", includes radicals having alkyl radicals, as defined herein, attached to a carbonyl radical. Examples of such radicals include substituted or unsubstituted methylcarbonyl, ethylcarbonyl, propylcarbonyl, butylcarbonyl, and pentylcarbonyl. The term "aralkyl" embraces aryl-substituted alkyl radicals. Preferred are "lower aralkyl" radicals having branched or unbranched lower alkyl portions containing one to six carbon atoms. Examples include benzyl, diphenylmethyl, triphenylmethyl, phenylethyl, and diphenylethyl. The aryl in said aralkyl may be additionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy. The terms benzyl and phenylmethyl are interchangeable. The term "aryloxy" embraces aryl radicals attached through an oxygen atom to other radicals. The term "aralkoxy" embraces aralkyl radicals attached through an oxygen atom to other radicals.

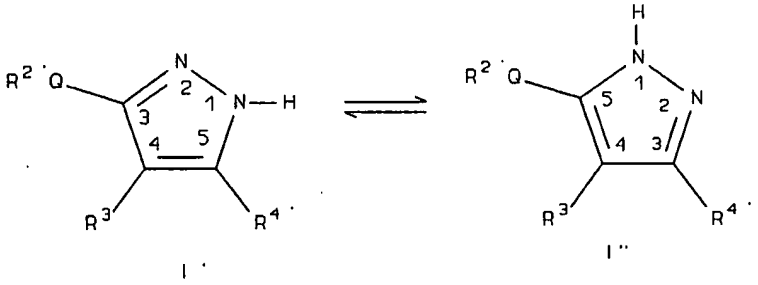
The term "aminoalkyl" embraces alkyl radicals substituted with amino radicals. More preferred are "lower aminoalkyl" radicals. Examples of such radicals include aminomethyl, aminoethyl, and the like. The term "alkylamino" denotes amino groups which are substituted with one or two alkyl radicals. Preferred are "lower alkylamino" radicals having alkyl portions having one to six carbon atoms. Suitable lower alkylamino may be monosubstituted N-alkylamino or disubstituted N,N-alkylamino, such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino or the like. The term "arylamino" denotes amino groups which are substituted with one or two aryl radicals, such as N-phenylamino. The "arylamino" radicals may be further substituted on the aryl ring portion of the radical. The term "aminocarbonyl" denotes an amide group of the formula -

$C(=O)NH_2$. The term "alkylaminocarbonyl" denotes an aminocarbonyl group which has been substituted with one or two alkyl radicals on the amino nitrogen atom. Preferred are "N-alkylaminocarbonyl" and "N,N-dialkylaminocarbonyl" radicals. More preferred are "lower N-alkylaminocarbonyl" and "lower N,N-dialkylaminocarbonyl" radicals with lower alkyl portions as defined above. The term "alkylcarbonylamino" embraces amino groups which are substituted with an alkylcarbonyl radical. More preferred alkylcarbonylamino radicals are "lower alkylcarbonylamino" having lower alkylcarbonyl radicals as defined above attached to amino radicals. The term "alkylaminoalkylene" embraces radicals having one or more alkyl radicals attached to an aminoalkyl radical.

The additional terms used to describe the substituents of the pyrazole ring and not specifically defined herein are defined in a similar manner to that illustrated in the above definitions. As above, more preferred substituents are those containing "lower" radicals. Unless otherwise defined to contrary, the term "lower" as used in this application means that each alkyl radical of a pyrazole ring substituent comprising one or more alkyl radicals has one to about six carbon atoms; each alkenyl radical of a pyrazole ring substituent comprising one or more alkenyl radicals has two to about six carbon atoms; each alkynyl radical of a pyrazole ring substituent comprising one or more alkynyl radicals has two to about six carbon atoms; each cycloalkyl or cycloalkenyl radical of a pyrazole ring substituent comprising one or more cycloalkyl and/or cycloalkenyl radicals is a 3 to 8 membered ring cycloalkyl or cycloalkenyl radical, respectively; each aryl radical of a pyrazole ring substituent comprising one or more aryl radicals is a monocyclic aryl radical; and each heterocyclyl radical of a pyrazole ring substituent

comprising one or more heterocyclyl radicals is a 4-8 membered ring heterocyclyl.

The present invention comprises the tautomeric forms of compounds of Formulas I-VIII. As illustrated below, the pyrazoles of Formula I' and I'' are magnetically and structurally equivalent because of the prototropic tautomeric nature of the hydrogen:



I' I''

The present invention also comprises compounds of Formula I-VIII having one or more asymmetric carbons. It is known to those skilled in the art that those pyrazoles of the present invention having asymmetric carbon atoms may exist in diastereomeric, racemic, or optically active forms. All of these forms are contemplated within the scope of this invention. More specifically, the present invention includes enantiomers, diastereomers, racemic mixtures, and other mixtures thereof.

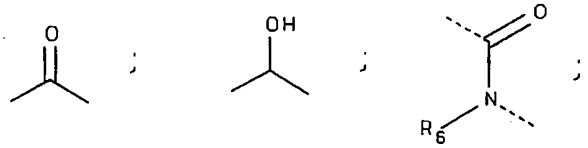
The present invention comprises a pharmaceutical composition for the treatment of a TNF mediated disorder, a p38 kinase mediated disorder, inflammation and/or arthritis, comprising a therapeutically-effective amount of a compound of Formula I-VIII, or a therapeutically-acceptable salt or tautomer thereof, in association with at least one pharmaceutically-acceptable carrier, adjuvant or diluent.

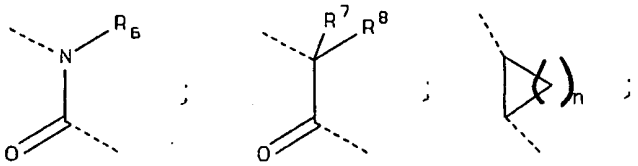
The present invention also comprises a therapeutic method of treating a TNF mediated disorder, a p38 kinase mediated disorder, inflammation and/or arthritis in a subject, the method comprising treating a subject having or susceptible to such disorder or condition with a

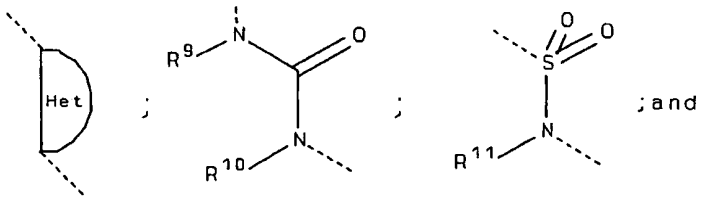
therapeutically-effective amount of a compound of Formula I, or a therapeutically-acceptable salt or tautomer thereof, wherein

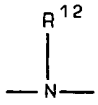
R^1 is selected from hydrido, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heterocyclyl, cycloalkylalkylene, cycloalkenylalkylene, haloalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, aralkyl, aralkenyl, aralkynyl, heterocyclylalkylene, alkoxyalkyl, aryloxyalkyl, heterocyclyloxyalkyl, mercaptoalkyl, mercaptoaryl, mercaptoheterocyclyl, alkylthioalkylene, arylthioalkylene, amino, alkylamino, arylamino, aminoalkyl, aminoaryl, alkylaminoalkylene, and heterocyclylalkylene; and

Q is selected from oxy, thio, alkylene, alkenylene, alkynylene, sulfinyl, sulfonyl,

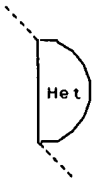








wherein



represents a four to eight membered ring heterocyclylidenyl comprising one or more heteroatoms selected from oxygen, sulfur and nitrogen; and

wherein n is an integer from 1 to 7; and

R^2 is aryl optionally substituted with one or more radicals independently selected from halo, alkyl, alkenyl, alkynyl, aryl, heterocyclyl, alkoxy, alkenoxy, alkynoxy, aryloxy, heterocyclyloxy, aralkoxy, alkylthio, arylthio, alkylsulfinyl, arylsulfinyl, alkylsulfonyl, arylsulfonyl, amino, alkylamino, alkenylamino, alkynylamino, arylamino, heterocyclylamino, aminoalkyl, aminocarbonyl, cyano, hydroxyl, hydroxyalkyl, alkoxycarbonyl, aryloxycarbonyl, heterocyclyloxycarbonyl, formyl, nitro, nitroalkyl, alkylcarbonylamino, arylcarbonylamino, haloalkylsulfinyl, haloalkylsulfonyl, alkylcarbonyl, arylcarbonyl, heterocyclylcarbonyl, and haloalkyl; and

R^3 is heteroaryl optionally substituted with one or more radicals independently selected from halo, alkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, amino, aminocarbonyl, cyano, hydroxyl, alkoxycarbonyl, formyl, aralkyl, aralkyloxy, aralkylthio, aralkylamino, aminosulfonyl, alkylamino, nitro, arylamino, alkylcarbonylamino, halosulfonyl, aminoalkyl, haloalkyl and alkylcarbonyl; and

R^4 is selected from hydrido, alkyl, aryl, haloalkyl, heterocyclyl, cycloalkyl, alkenyl, cycloalkenyl, alkoxy, alkylthio, arylthio, carboxy, alkoxycarbonyl, carboxyalkyl, alkoxycarbonylalkylene, heterocyclylalkyl, amino, alkylamino, alkynylamino, arylamino, heterocyclylamino, heterocyclylalkylamino,

heterocyclylaminoalkyl, and aminoheterocyclylamino; wherein the aryl, heterocyclyl, cycloalkyl, cycloalkenyl groups are optionally substituted with one or more radicals independently selected from halo, amino, alkyl, alkenyl, alkynyl, alkoxy, aryloxy, aralkoxy, haloalkyl, and alkylamino; and wherein the amino radicals of the heterocylcylalkylamino and heterocylcylaminoalkyl group are optionally substituted with one or more alkyl; and

R^6 is selected from hydrido, alkyl, alkenyl, and alkynyl; and

R^7 and R^8 are independently selected from hydrido, alkyl, alkenyl, and alkynyl, or together form a carbocyclic or heterocyclic ring having three to eight members; and

R^9 is selected from hydrido, alkyl, alkenyl, and alkynyl; and

R^{10} is selected from hydrido, alkyl, alkenyl, and alkynyl; and

R^{11} is selected from hydrido, alkyl, alkenyl, and alkynyl; and

R^{12} is selected from hydrido and alkyl; or

a pharmaceutically-acceptable salt or tautomer thereof.

Also included in the family of compounds of Formula I are the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds of Formula I may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric

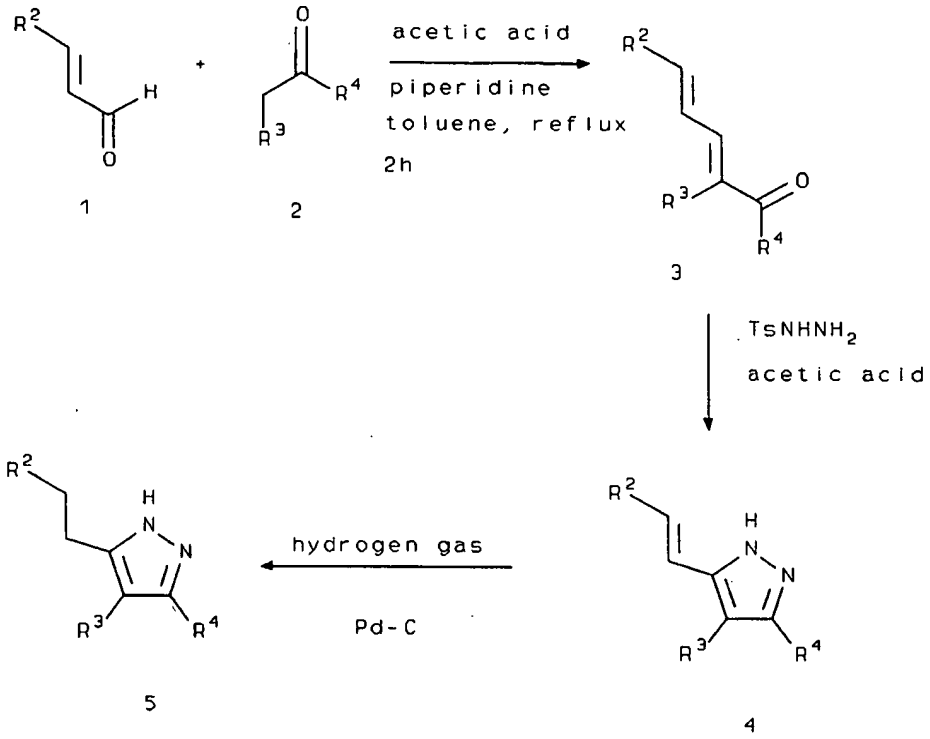
acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclyl, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, stearic, salicylic, *p*-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, cyclohexylaminosulfonic, algenic, β-hydroxybutyric, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formula I include metallic salts and organic salts. More preferred metallic salts include, but are not limited to appropriate alkali metal (group Ia) salts, alkaline earth metal (group IIa) salts and other physiological acceptable metals. Such salts can be made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc. Preferred organic salts can be made from tertiary amines and quaternary ammonium salts, including in part, tromethamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound of Formulas I-VIII by reacting, for example, the appropriate acid or base with the compound of Formulas I-VIII.

General Synthetic Procedures

The compounds of the invention can be prepared according to the following procedures of Schemes I-X wherein the R^1-R^{11} and Q substituents are as previously

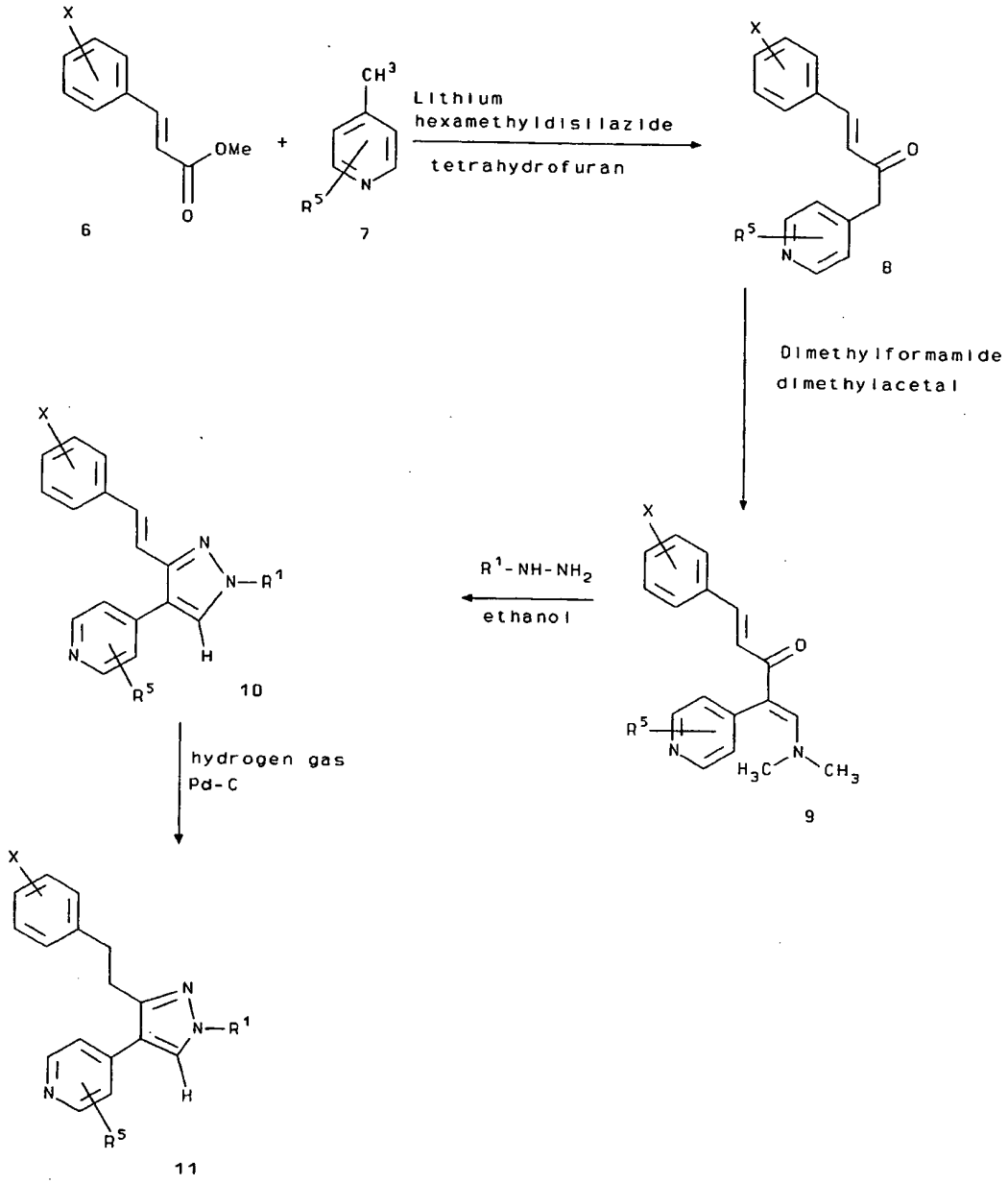
defined for compounds of Formula I or II except where noted.

SCHEME I



General Synthetic Scheme I shows the preparation of the pyrazoles of the present invention where R^1 is hydrido and where Q is a saturated alkylene bridging radical **5** or an unsaturated alkenylene bridge **4**. A propenyl derivative **1** is condensed with heterocyclic ketones and aldehydes **2** by the Knoevenagle condensation to give the pictured dienone **3**. The dienone **3** is condensed, such as with tosyl hydrazide in boiling acetic acid, to yield the corresponding pyrazole derivative **4** of the present invention (where R^1 is hydrido, Q is alkenylene). Other compounds of the invention **5** (where Q is alkylene) can be prepared from pyrazole **4** via hydrogenation of the double bond, such as with hydrogen gas and palladium on carbon in a suitable solvent, such as methanol.

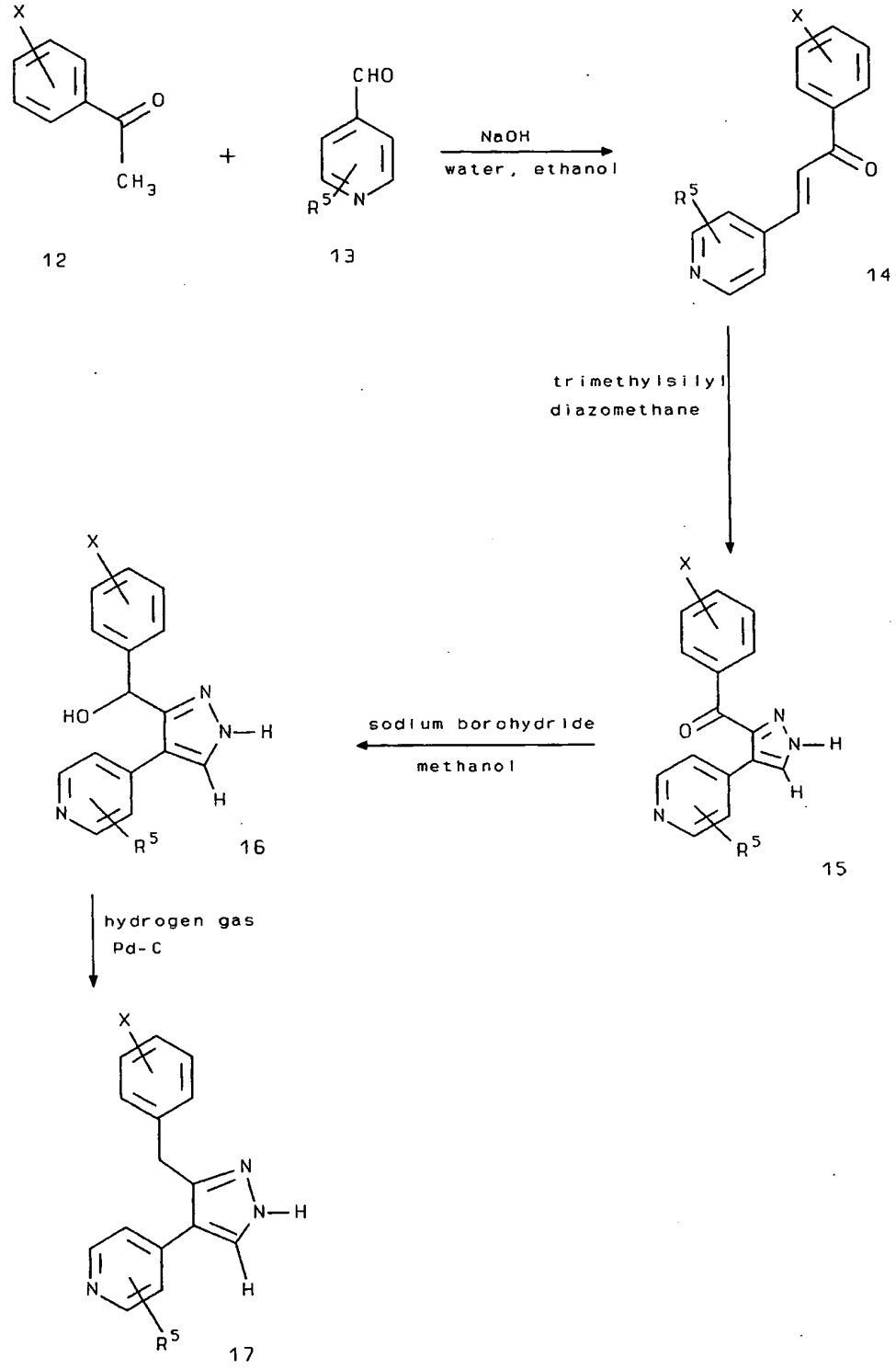
SCHEME II



General Synthetic Scheme II shows the preparation of a subset of the pyrazoles of the present invention (where R^2 is optionally substituted phenyl, R^3 is optionally substituted pyridyl, and R^4 is hydrido) where Q is a saturated alkylene bridging radical **11** or an unsaturated alkenylene bridge **10**. A cinnamic ester **6** is alkylated

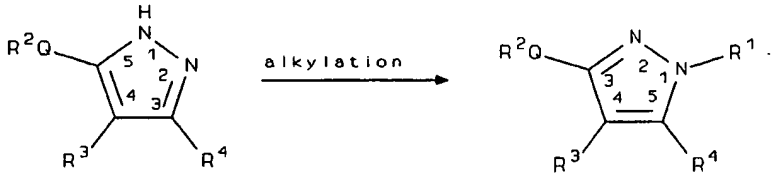
with the anion of 4-picoline **7**, such as by treatment with lithium hexamethyldisilazide (or other suitable base, such as sodium hydride) to the pictured enone **8**. Reaction of the enone **8** with dimethylformamide dimethyl acetal gives the pictured vinylamine **9**, which upon reaction with a suitable hydrazine yields the pyrazole **10** having an unsaturated alkenylene bridging radical. The unsaturated pyrazole **10** can be reduced to the corresponding saturated pyrazole **11**, such as with hydrogen gas in the presence of palladium on carbon.

SCHEME III


X
O
CH3
12
+
CHO
R5
N
13
NaOH
water, ethanol
X
O
R5
N
14
trimethylsilyl
diazomethane
X
O
N
N—H
H
N
R5
15
sodium borohydride
methanol
X
HO
N
N—H
H
N
R5
16
hydrogen gas
Pd-C
X
N
N—H
H
N
R5
17

General Synthetic Scheme III shows the preparation of a subset of the pyrazoles of the present invention (where R^1 is hydrido, R^2 is optionally substituted phenyl, R^3 is optionally substituted pyridyl, R^4 is hydrido) where Q is a carbonyl radical **15**, a hydroxy-substituted alkylene bridge **16**, or a saturated methylene bridging radical **17**. Suitable acetophenone derivatives **12** are condensed with optionally substituted pyridines **13** in the presence of base to form enones **14**. Cyclization of enone **14**, such as with trimethylsilyldiazomethane, according to the published procedure of Aoyama, et al. (*Chem. Pharm. Bull.*, **37**, 253-256 (1989)) gives the pictured pyrazole-ketone **15**. Other compounds of the invention are produced from the ketone **15**, such as by reduction with sodium borohydride in methanol to form the alcohols **16**. The alcohols **16** may be hydrogenolyzed by the action of hydrogen gas and palladium on carbon to form the pyrazoles **17** (where Q is methylene).

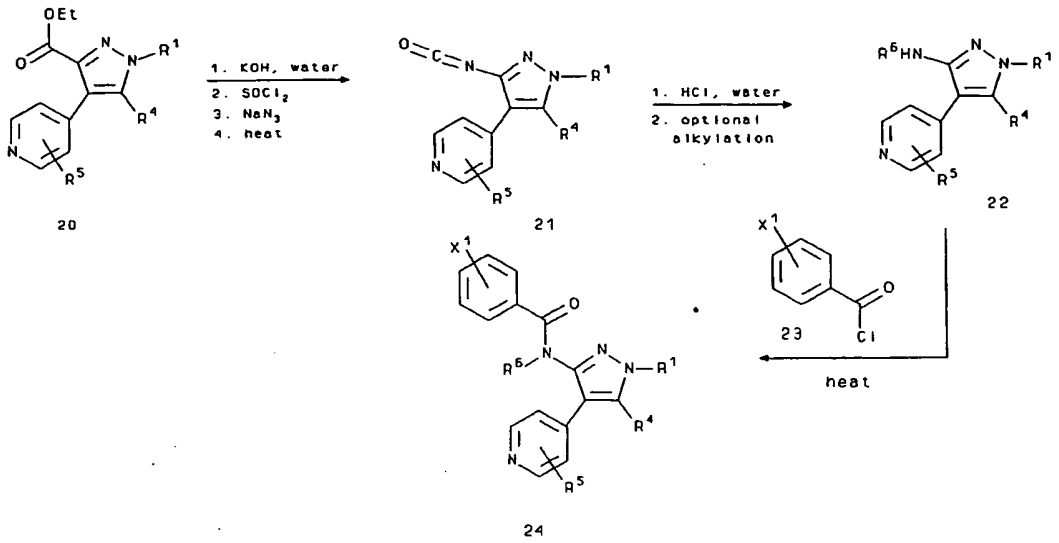
SCHEME IV



18 19

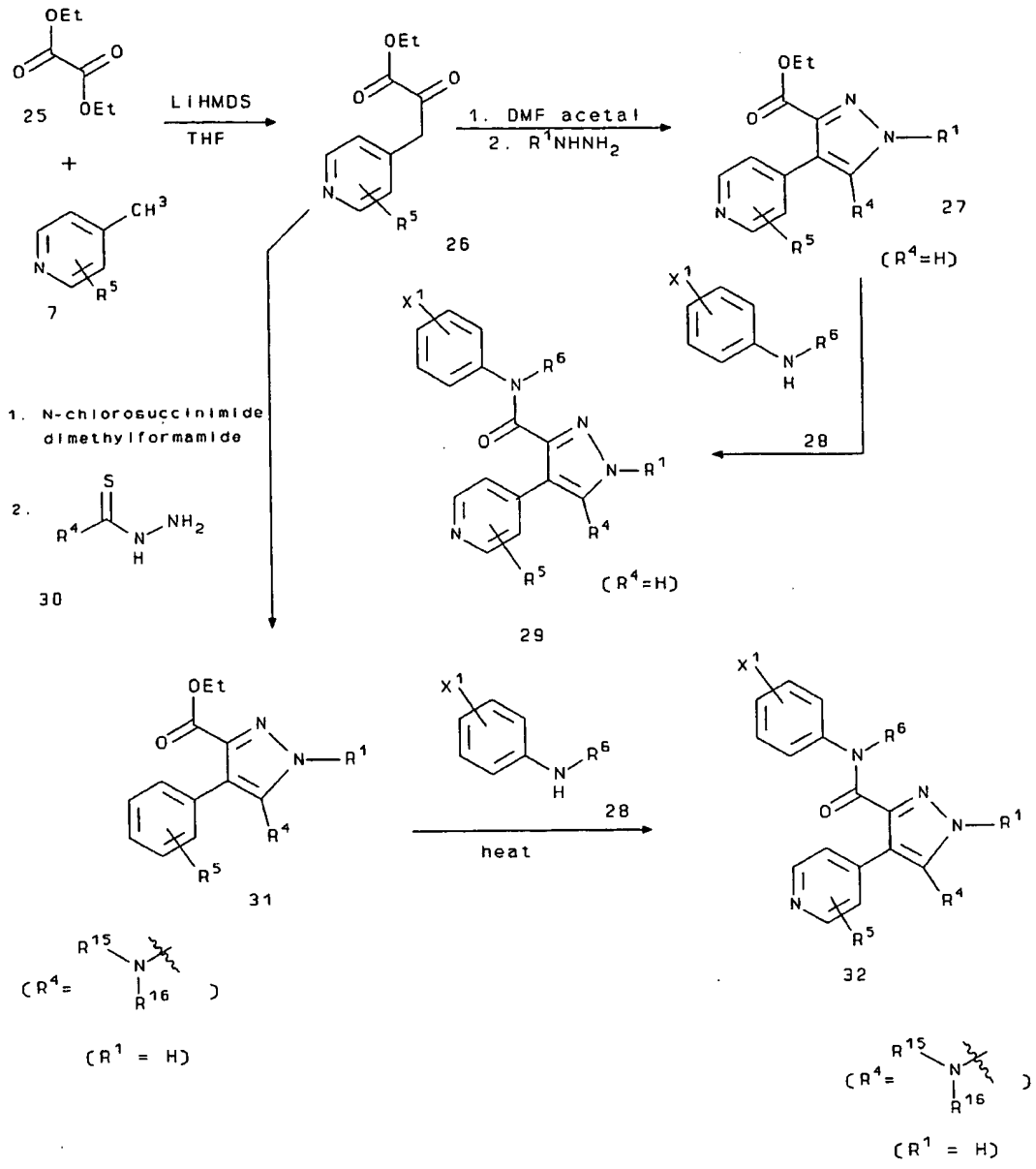
General Synthetic Scheme IV shows the preparation of the pyrazoles of the present invention where R^1 is alkyl or substituted alkyl. The pyrazole derivatives **18** can be alkylated at pyrazole position 1 with a suitable base, such as sodium hydride or potassium carbonate, in a suitable solvent, such as dimethylformamide, to yield the corresponding alkylated pyrazole derivatives **19**.

SCHEME V



General Synthetic Scheme V shows the preparation of a subset of the pyrazoles of the present invention where Q is an amide bridging radical. Ester **20** (prepared as set forth in Scheme VI) is hydrolyzed to the corresponding acid, then converted to an acid halide, for example by treatment with thionyl chloride. The acid halide is treated with a suitable alkali azide, such as sodium azide, and the resulting azide heated to effect the Curtius rearrangement to isocyanate **21**. Isocyanate **21** is hydrolyzed with aqueous acid to yield free amine **22**, which can be optionally alkylated to introduce the R^6 substitution. Amine **22** is then acylated with a suitable aromatic active ester or acid halide **23** (preferably an aromatic active ester or acid chloride) to give pyrazoles **24**.

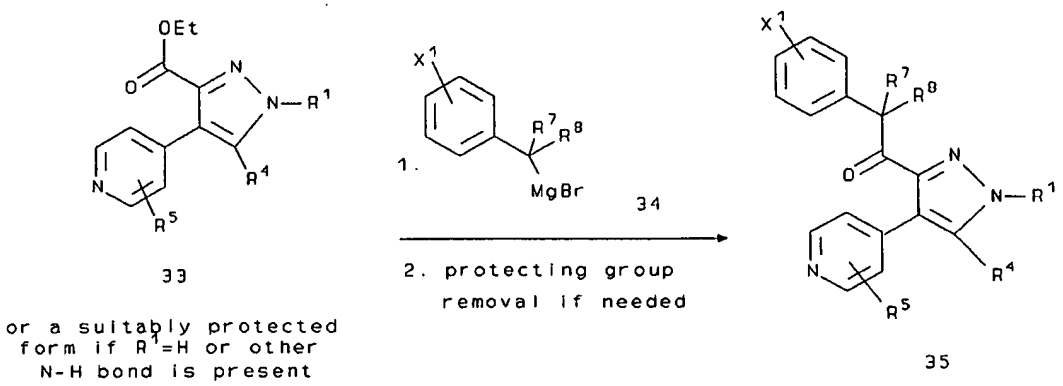
SCHEME VI


OEt
25
OEt
LiHMDS
THF
CH3
7
OEt
26
1. DMF acetal
2. R1NHNH2
OEt
27
(R4=H)
28
1. N-chlorosuccinimide
dimethylformamide
2.
30
29
(R4=H)
OEt
31
28
heat
32
(R1 = H)
(R1 = H)

General Synthetic Scheme VI shows the preparation of a subset of the pyrazoles of Formula I where Q is an amide bridging radical. Optionally substituted 4-picoline **7** is deprotonated with a strong base, such as lithium hexamethyldisilazide, and acylated, for example, with oxalate ester **25** to give pyruvate **26**. Pyruvate **26** is reacted with dimethylformamide dimethyl acetal to give an intermediate vinyl amine that is reacted with an optionally substituted hydrazine to give pyrazole ester **27**. Pyrazole ester **27** is treated with aniline **28**, under the influence of heat, to give pyrazole **29** wherein R^4 is preferably hydrido. Alternatively, pyrazole ester **27** instead can be hydrolyzed to an intermediate acid which is then coupled to aniline **28** using a conventional amide coupling reaction (such as the coupling reaction of pyrazole ester **27** with dicyclohexylcarbodiimide).

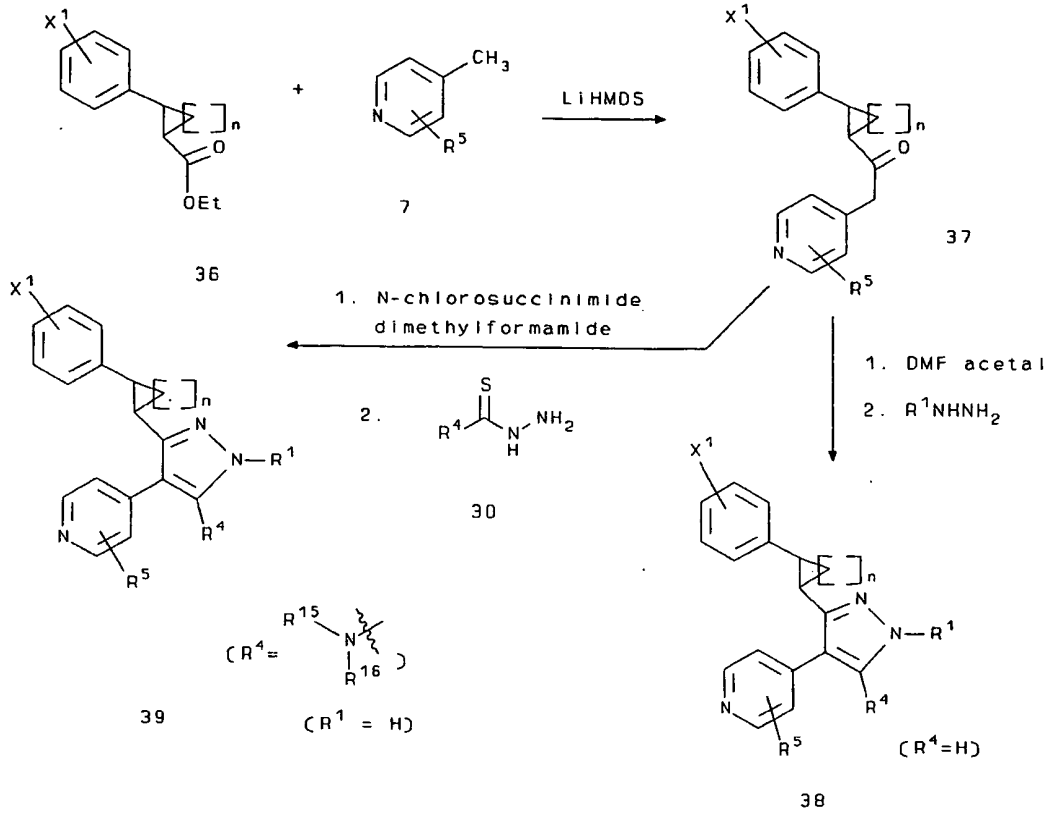
Pyruvate **26** also may be treated with a halogenating agent, such as N-chlorosuccinimide, to yield an intermediate haloketone that is then reacted with thiosemicarbazide **30** to form pyrazole **31**. Pyrazole **31** is aminated with aniline **28** using the procedure described above to produce aminopyrazole **32** wherein R^1 is hydrido, R^4 is $-NR^{15}R^{16}$, and R^{15} and R^{16} are, for example, hydrogen or alkyl, or together with the nitrogen atom to which they are attached form a 4 to 8 membered ring heterocyclyl comprising at least one heteroatom selected from oxygen, sulfur and nitrogen. The R^1 hydrido of aminopyrazole **32** can be replaced with other substituents as shown, for example, in Scheme IV.

SCHEME VII



General Synthetic Scheme VII shows the preparation of a subset of the pyrazoles of Formula I where Q is an ethanone bridging radical. Ester **33** (prepared as set forth in Scheme VI) is treated with a Grignard reagent **34** to produce pyrazole **35**. Ester **33** may be suitably protected, employing protecting groups known to those skilled in the art, to efficiently carry out this transformation.

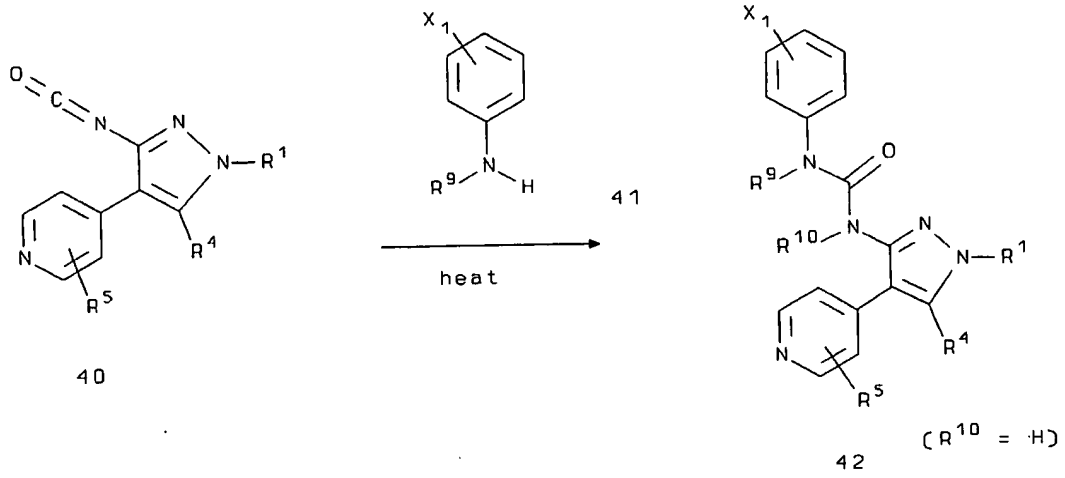
SCHEME VIII



General Synthetic Scheme VIII shows the preparation of a subset of the pyrazoles of Formula I where Q is a cyclic bridging radical. Optionally substituted 4-picoline **7** is deprotonated with a strong base, such as lithium hexamethyldisilazide, and acylated with cyclic ester **36** to give ketone **37**. Ketone **37** is reacted with dimethylformamide dimethyl acetal to give intermediate vinyl amine that is reacted with optionally substituted hydrazine to give pyrazole **38** wherein R^4 is hydrido.

Alternatively, ketone **37** can be halogenated to form an intermediate haloketone that can be reacted with optionally substituted thiosemicarbazide **30** to give pyrazole **39** wherein R^1 is hydrido, R^4 is $-NR^{15}R^{16}$, and R^{15} and R^{16} are as defined for Scheme VI.

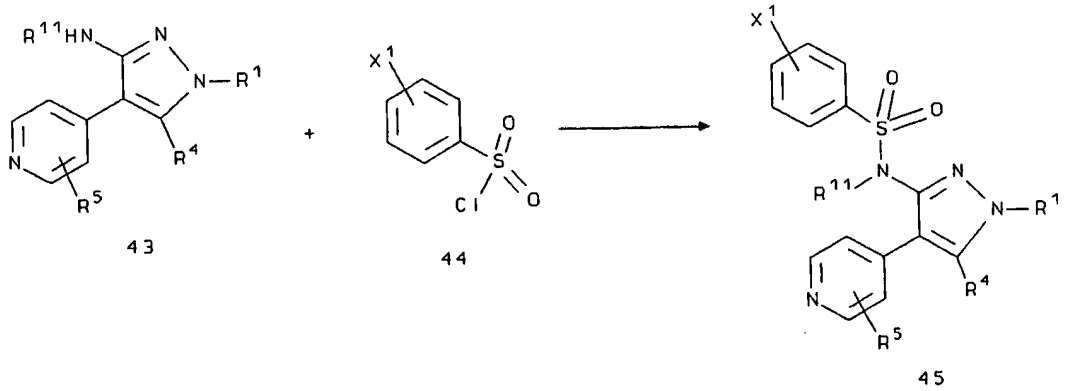
SCHEME IX



40 41 42 (R^{10} = H)

General Synthetic Scheme IX shows the preparation of a subset of the pyrazoles of Formula I where Q is a urea bridging radical. Isocyanate **40** (prepared as set forth in Scheme V) is reacted with optionally substituted aniline **41** to give urea **42**.

SCHEME X

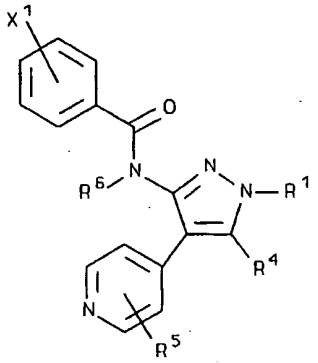


43 44 45

General Synthetic Scheme X shows the preparation of a subset of the pyrazoles of Formula I where Q is a sulfonamide bridging radical. Amine **43** (prepared as set

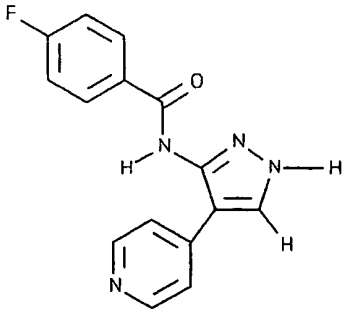
forth in Scheme V) is reacted with an optionally substituted aromatic sulfonyl halide **44**, preferably sulfonyl chloride, to give pyrazole **45**.

Within Formula I there is another subclass of compounds of interest represented by Formula III:

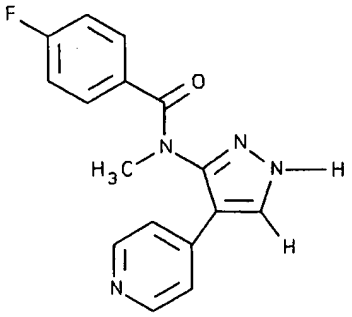


(III)

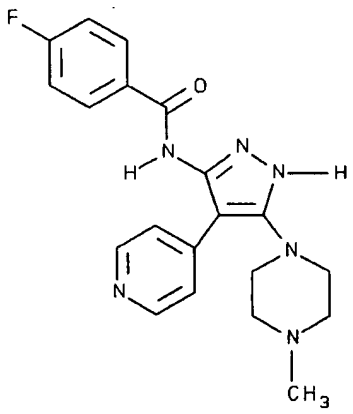
Compounds of Formula III can be prepared in accordance with the chemistry set forth above (particularly Scheme V) and include the following compounds:



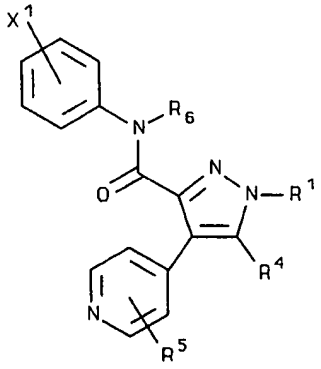
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; and

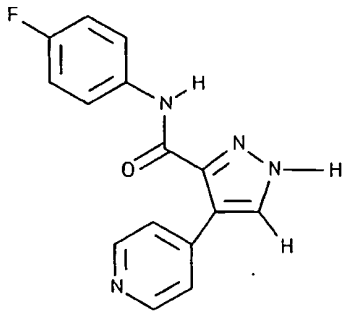


Within Formula I there is another subclass of compounds of interest represented by Formula IV:

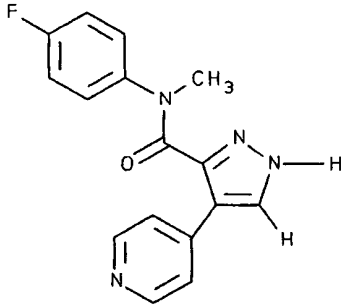


(IV)

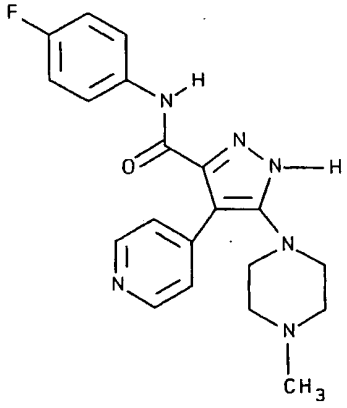
Compounds of Formula IV can be prepared in accordance with the chemistry set forth above (particularly Scheme VI) and include the following compounds:



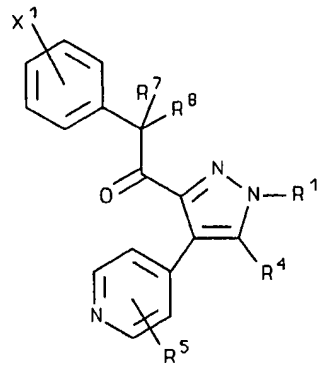
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; and

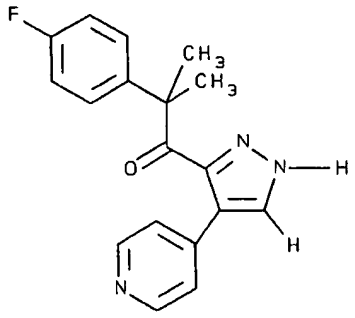


Within Formula I there is another subclass of compounds of interest represented by Formula V:

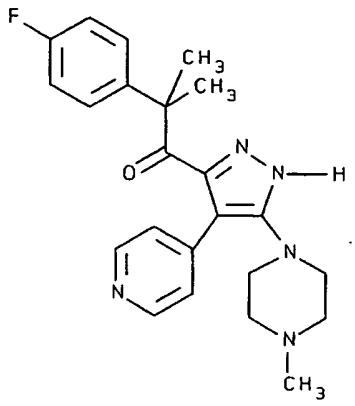


(V)

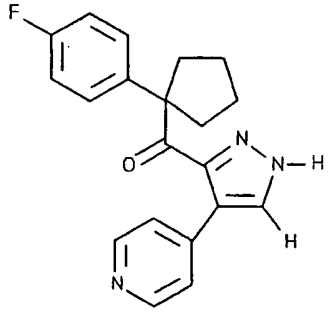
Compounds of Formula V can be prepared in accordance with the chemistry set forth above (particularly Scheme VII) and include the following compounds:



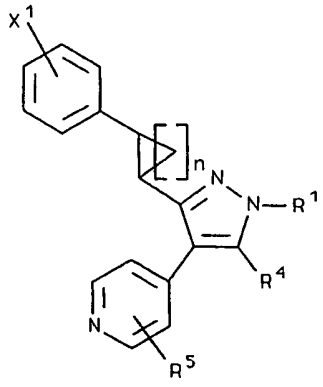
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;

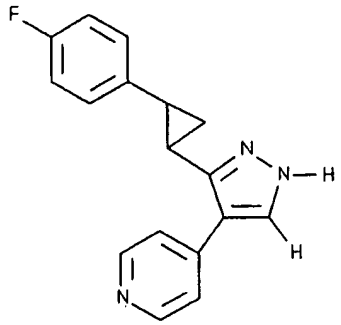


Within Formula I there is another subclass of compounds of interest represented by the Formula VI:

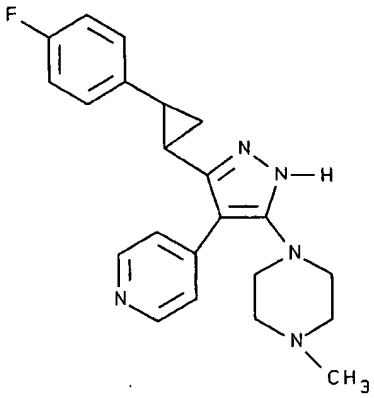


(VI)

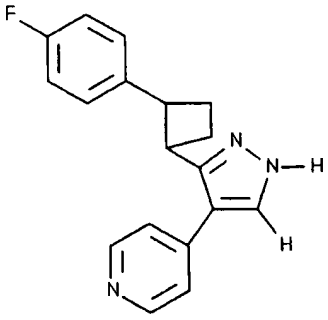
Compounds of Formula VI can be prepared in accordance with the chemistry set forth above (particularly Scheme VIII) and include the following compounds:



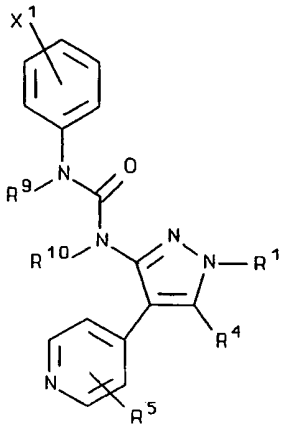
;



; and

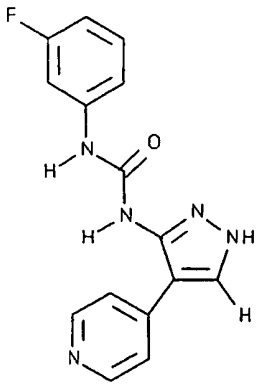


Within Formula I there is another subclass of compounds of interest represented by Formula VII:

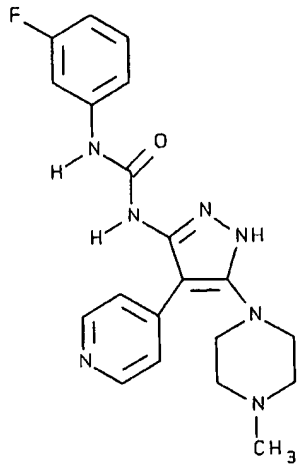


(VII)

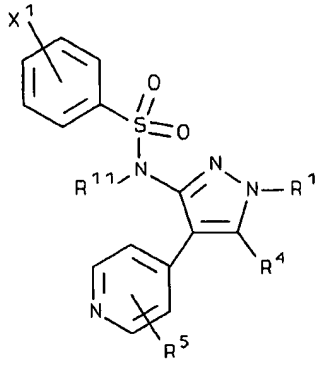
Compounds of Formula VII can be prepared in accordance with the chemistry set forth above (particularly Scheme IX) and include the following compounds:



; and

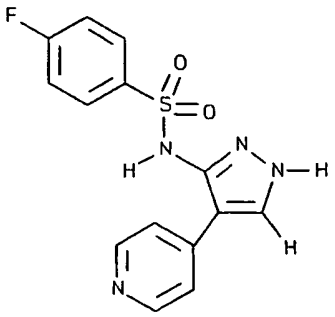


Within Formula I there is another subclass of compounds of interest represented by Formula VIII

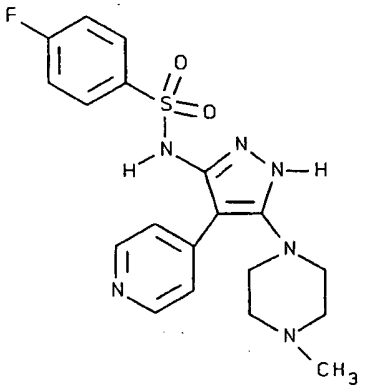


(VIII)

Compounds of Formula VIII can be prepared in accordance with the chemistry set forth above (particularly Scheme X) and include the following compounds:



; and



In the above compounds of Formula III, IV, V, VI, VII and VIII, the substituents R^1, R^4, R^5, R^6, R^7, R^8, R^9, R^{10} and R^{11} are as previously defined for the compounds of Formula I, and substituent X^1 encompasses the optional substituents previously defined for the R^2 aryl group of the compounds of Formula I. In addition to the specific compounds illustrated above, other specific compounds of Formula III, IV, V, VI, VII and VIII of particular interest include those wherein the R^4 hydrogen or methylpiperazinyl substituent is replaced with propargylamino, substituted or unsubstituted piperidinyl, or substituted or unsubstituted morpholinyl.

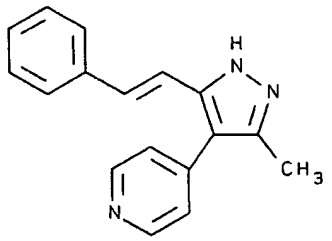
The following examples contain detailed descriptions of the methods of preparation of compounds of Formula I-VIII. These detailed descriptions fall within the scope, and serve to exemplify, the above described General Synthetic Procedures which form part of the invention. These detailed descriptions are presented for illustrative purposes only and are not intended as a restriction on the scope of the invention. All parts are by weight and temperatures are in Degrees centigrade unless otherwise indicated. All compounds showed NMR spectra consistent with their assigned structures. In some cases, the assigned structures were confirmed by nuclear Overhauser effect (NOE) experiments.

The following abbreviations are used:

MeOH - methanol
Pd/C - palladium on carbon
RT - room temperature
DTT - dithiotreitol
dH_2O - distilled water
PBS - phosphate buffered saline
NaCl - sodium chloride
KCl - potassium chloride
Na_2HPO_4 - sodium phosphate
KH_2PO_4 - potassium phosphate
PMSF - phenylmethylsulfonyl fluoride
EDTA - ethylene diamine tetraacetic acid
HEPES - N-[2-hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid]
DMSO - dimethyl sulfoxide
$SOCl_2$ - thionyl chloride
NaN_3 - sodium azide
KOH - potassium hydroxide
Et - ethyl
LiHMDS - lithium hexamethyldisilazide
THF - tetrahydrofuran

DMF - dimethyl formamide
h - hour
min - minutes

EXAMPLE 1



4-[3-Methyl-5-(2-phenylethenyl)-1H-pyrazol-4-yl]pyridine

Step 1: Preparation of 6-phenyl-3-(4-pyridinyl)hexa-3,5-dien-2-one

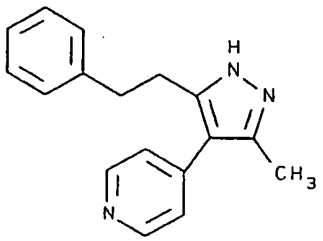
Trans-cinnamaldehyde (1.84 ml, 14.8 mmol), five drops of piperidine and five drops of acetic acid were added to a solution of 4-pyridyl acetone (2.0 g, 14.8 mmol) in toluene (25 ml). The mixture was heated to reflux for 48 hours with a Dean-Stark trap to remove water. The mixture was concentrated to give a black oil. The oil was purified by silica gel chromatography (eluted with 1:1 hexane/ethyl acetate). The desired fractions were collected, combined and concentrated to give 6-phenyl-3-(4-pyridinyl)hexa-3,5-dien-2-one (628 mg). The ketone was further purified by an additional column chromatography on silica gel (eluting with hexane-ethyl acetate-methylene chloride-methanol (1 : 1 : 2 : 0.12)) (380 mg, 27.3%): Anal. Calc'd for $C_{17}H_{15}NO$ 0.4 H_2O: C, 79.91; H, 5.84; N, 5.48. Found: C, 79.72; H, 5.91; N, 5.25. MS ($M+H^+$): 250.

Step 2: Preparation of 4-[3-methyl-5-(2-phenylethenyl)-1H-pyrazol-4-yl]pyridine

A solution of 6-phenyl-3-(4-pyridinyl)hexa-3,5-dien-2-one (step 1) (0.38 g, 1.52 mmol) and p-toluenesulfonyl hydrazide (0.28 g, 1.52 mmol) in acetic acid (3 ml) was heated to reflux for 48 hours. The mixture was concentrated and purified by silica gel chromatography (eluting with 1:1 hexane/ethyl acetate). The desired

fractions were collected, combined and concentrated to give 4-[3-methyl-5-(2-(phenylethenyl)-1H-pyrazol-4-yl]pyridine as an off-white solid (26 mg, 6.5%): Anal. Calc'd for $C_{17}H_{15}N_3 \bullet 0.75\ H_2O$: C, 74.54; H, 6.03; N, 15.34. Found: C, 74.66; H, 5.69; N, 15.08. MS ($M+H^+$): 262 (100%).

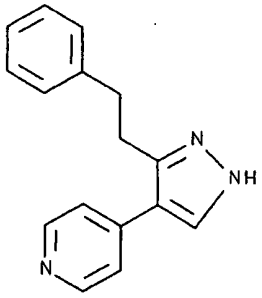
EXAMPLE 2



4-[3-Methyl-5-(2-phenylethyl)-1H-pyrazol-4-yl]pyridine

4-(3-Methyl-5-(2-phenylethenyl)-1H-pyrazol-4-yl)pyridine (Example 1) (0.177 g, 0.67 mmol) was hydrogenated (5-30 psi) in MeOH in the presence of a catalytic amount of 4% Pd/C at RT for 12 hours. The resulting mixture was filtered and the resulting solution was concentrated to give 4-(3-methyl-5-phenylethyl-1H-pyrazol-4-yl)pyridine quantitatively: MS ($M+H^+$) 264 (100%).

EXAMPLE 3



4-[5-(2-phenylethyl)-1H-pyrazol-4-yl]pyridine

To a solution of lithium bis(trimethylsilyl)amide (100 mL, 1M, 100 mmol) in THF was added 4-picoline (9.73 mL, 100 mmol) at -10 °C. The mixture was warmed to 0 °C and held at this temperature for 1 hour. Ethyl hydrocinnamate (8.82 mL, 50 mmol) was added slowly to the mixture at 0 °C. The solution was stirred at 25 °C overnight. The mixture was concentrated, diluted with H_2O (100 mL), neutralized with concentrated HCl to pH = 8, and extracted with ethyl acetate (150 mL). The organic layer was washed with H_2O (100 mL x 2), brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give a yellow oil (11.2 g, 100% yield).

To the above oil (5.6 g, 25 mmol) dissolved in tetrahydrofuran (30 mL) was added N,N-dimethylformamide dimethyl acetal (13 mL, 98 mmol) and the solution was stirred at room temperature for 48 hours. The solution was concentrated and dissolved in ethyl acetate (100 mL). The organic layer was washed with H_2O (50 mL x 2), brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give a yellow oil (2.6g, 37% yield). The oil (1.6 g) was purified by column chromatography on silica gel to give a pure product (0.36g, 22%).

The above product (0.36 g, 1.3 mmol), hydrazine hydrate (0.4 mL, 12.7 mmol) and methanol (2 mL) were mixed and stirred at 25 °C overnight. The mixture was concentrated and dissolved in ethyl acetate (20 mL). The organic layer was washed with H_2O (10 mL x 2), brine (10 mL), dried over $MgSO_4$, filtered and concentrated to give an oil. The oil (1.6 g) was purified by column chromatography on silica gel to give 4-[5-(2-phenylethyl)-1H-pyrazol-4-yl]pyridine (0.1g, 31.6% yield). mp: 125-131 0C; mass spectrum (m/z): 250 (M+1). Anal. calc'd for $C_{16}H_{15}N_3$: C, 77.08; H, 6.28; N, 16.86. Found: C, 76.72; H, 6.28; N, none.

BIOLOGICAL EVALUATION

p38 Kinase Assay

Cloning of human p38a:

The coding region of the human p38a cDNA was obtained by PCR-amplification from RNA isolated from the human monocyte cell line THP.1. First strand cDNA was synthesized from total RNA as follows: 2 μg of RNA was annealed to 100 ng of random hexamer primers in a 10 μl reaction by heating to 70 °C for 10 minutes followed by 2 minutes on ice. cDNA was then synthesized by adding 1 μl of RNAsin (Promega, Madison WI), 2 μl of 50 mM dNTP's, 4 μl of 5X buffer, 2 μl of 100 mM DTT and 1 μl (200 U) of Superscript II ™ AMV reverse transcriptase. Random primer, dNTP's and Superscript ™ reagents were all purchased from Life-Technologies, Gaithersburg, MA. The reaction was incubated at 42 °C for 1 hour. Amplification of p38 cDNA was performed by aliquoting 5 μl of the reverse transcriptase reaction into a 100 μl PCR reaction containing the following: 80 μl dH_2O, 2 μl 50 mM dNTP's, 1 μl each of forward and reverse primers (50 pmol/μl), 10 μl of 10X buffer and 1 μl Expand ™ polymerase (Boehringer Mannheim). The PCR primers incorporated Bam HI sites onto the 5' and 3' end of the amplified fragment, and were purchased from Genosys. The sequences of the forward and reverse primers were

5'-GATCGAGGATTCATGTCTCAGGAGAGGCCCA-3' and

5'GATCGAGGATTCTCAGGACTCCATCTCTTC-3' respectively.

The PCR amplification was carried out in a DNA Thermal Cycler (Perkin Elmer) by repeating 30 cycles of 94 °C for 1 minute, 60 °C for 1 minute and 68 °C for 2 minutes. After amplification, excess primers

and unincorporated dNTP's were removed from the amplified fragment with a Wizard ™ PCR prep (Promega) and digested with Bam HI (New England Biolabs). The Bam HI digested fragment was ligated into BamHI digested pGEX 2T plasmid DNA (PharmaciaBiotech) using T-4 DNA ligase (New England Biolabs) as described by T. Maniatis, *Molecular Cloning: A Laboratory Manual, 2nd ed.* (1989). The ligation reaction was transformed into chemically competent *E. coli* DH10B cells purchased from Life-Technologies following the manufacturer's instructions. Plasmid DNA was isolated from the resulting bacterial colonies using a Promega Wizard™ miniprep kit. Plasmids containing the appropriate Bam HI fragment were sequenced in a DNA Thermal Cycler (Perkin Elmer) with Prism™ (Applied Biosystems Inc.). cDNA clones were identified that coded for both human p38a isoforms (Lee et al. Nature 372, 739). One of the clones which contained the cDNA for p38a-2 (CSBP-2) inserted in the cloning site of pGEX 2T, 3' of the GST coding region was designated pMON 35802. The sequence obtained for this clone is an exact match of the cDNA clone reported by Lee et al. This expression plasmid allows for the production of a GST-p38a fusion protein.

Expression of human p38a:

GST/p38a fusion protein was expressed from the plasmid pMON 35802 in *E. coli*, stain DH10B (Life Technologies, Gibco-BRL). Overnight cultures were grown in Luria Broth (LB) containing 100 mg/ml ampicillin. The next day, 500 ml of fresh LB was inoculated with 10 ml of overnight culture, and grown in a 2 liter flask at 37 °C with constant shaking until the culture reached an absorbance of

0.8 at 600 nm. Expression of the fusion protein was induced by addition of isopropyl b-D-thiogalactosidse (IPTG) to a final concentration of 0.05 mM. The cultures were shaken for three hours at room temperature, and the cells were harvested by centrifugation. The cell pellets were stored frozen until protein purification.

Purification of p38 Kinase-α:

All chemicals were from Sigma Chemical Co. unless noted. Twenty grams of *E. coli* cell pellet collected from five 1 L shake flask fermentations was resuspended in a volume of PBS (140 mM NaCl, 2.7 mM KCl, 10 mM Na_2HPO_4, 1.8 mM KH_2PO_4, pH 7.3) up to 200 ml. The cell suspension was adjusted to 5 mM DTT with 2 M DTT and then split equally into five 50 ml Falcon conical tubes. The cells were sonicated (Ultrasonics model W375) with a 1 cm probe for 3 X 1 minutes (pulsed) on ice. Lysed cell material was removed by centrifugation (12,000 x g, 15 minutes) and the clarified supernatant applied to glutathione-sepharose resin (Pharmacia).

Glutathione-Sepharose Affinity Chromatography:

Twelve ml of a 50% glutathione sepharose-PBS suspension was added to 200 ml clarified supernatant and incubated batchwise for 30 minutes at room temperature. The resin was collected by centrifugation (600 x g, 5 min) and washed with 2 x 150 ml PBS/1% Triton X-100, followed by 4 x 40 ml PBS. To cleave the p38 kinase from the GST-p38 fusion protein, the glutathione-sepharose resin was resuspended in 6 ml PBS containing 250 units thrombin protease (Pharmacia, specific activity > 7500 units/mg) and mixed gently for 4 hours at room temperature. The glutathione-sepharose resin was

removed by centrifugation (600 x g, 5 min) and washed 2 x 6 ml with PBS. The PBS wash fractions and digest supernatant containing p38 kinase protein were pooled and adjusted to 0.3 mM PMSF.

Mono Q Anion Exchange Chromatography:

The thrombin-cleaved p38 kinase was further purified by FPLC-anion exchange chromatography. Thrombin-cleaved sample was diluted 2-fold with Buffer A (25 mM HEPES, pH 7.5, 25 mM beta-glycerophosphate, 2 mM DTT, 5% glycerol) and injected onto a Mono Q HR 10/10 (Pharmacia) anion exchange column equilibrated with Buffer A. The column was eluted with a 160 ml 0.1 M-0.6 M NaCl/Buffer A gradient (2 ml/minute flowrate). The p38 kinase peak eluting at 200 mM NaCl was collected and concentrated to 3-4 ml with a Filtron 10 concentrator (Filtron Corp.).

Sephacryl S100 Gel Filtration Chromatography:

The concentrated Mono Q- p38 kinase purified sample was purified by gel filtration chromatography (Pharmacia HiPrep 26/60 Sephacryl S100 column equilibrated with Buffer B (50 mM HEPES, pH 7.5, 50 mM NaCl, 2 mM DTT, 5% glycerol)). Protein was eluted from the column with Buffer B at a 0.5 ml/minute flowrate and protein was detected by absorbance at 280 nm. Fractions containing p38 kinase (detected by SDS-polyacrylamide gel electrophoresis) were pooled and frozen at -80 °C. Typical purified protein yields from 5 L *E. coli* shake flasks fermentations were 35 mg p38 kinase.

In Vitro Assay

The ability of compounds to inhibit human p38 kinase alpha was evaluated using two in vitro assay

methods. In the first method, activated human p38 kinase alpha phosphorylates a biotinylated substrate, PHAS-I (phosphorylated heat and acid stable protein-insulin inducible), in the presence of gamma ^{32}P-ATP (^{32}P-ATP). PHAS-I was biotinylated prior to the assay and provides a means of capturing the substrate which is phosphorylated during the assay. p38 Kinase was activated by MKK6. Compounds were tested in 10 fold serial dilutions over the range of 100 μM to 0.001 μM using 1% DMSO. Each concentration of inhibitor was tested in triplicate.

All reactions were carried out in 96 well polypropylene plates. Each reaction well contained 25 mM HEPES pH 7.5, 10 mM magnesium acetate and 50 μM unlabeled ATP. Activation of p38 was required to achieve sufficient signal in the assay. Biotinylated PHAS-I was used at 1-2 μg per 50 μl reaction volume, with a final concentration of 1.5 μM. Activated human p38 kinase alpha was used at 1 μg per 50 μl reaction volume representing a final concentration of 0.3 μM. Gamma ^{32}P-ATP was used to follow the phosphorylation of PHAS-I. ^{32}P-ATP has a specific activity of 3000 Ci/mmol and was used at 1.2 μCi per 50 μl reaction volume. The reaction proceeded either for one hour or overnight at 30 °C.

Following incubation, 20 μl of reaction mixture was transferred to a high capacity streptavidin coated filter plate (SAM-streptavidin-matrix, Promega) prewetted with phosphate buffered saline. The transferred reaction mix was allowed to contact the streptavidin membrane of the Promega plate for 1-2 minutes. Following capture of biotinylated PHAS-I with ^{32}P incorporated, each well was washed to remove unincorporated ^{32}P-ATP three times with 2M NaCl, three washes of 2M NaCl with 1% phosphoric, three washes of distilled water and finally a single

wash of 95% ethanol. Filter plates were air dried and 20 μl of scintillant was added. The plates were sealed and counted. Results are shown in Table 4.

A second assay format was also employed that is based on p38 kinase alpha induced phosphorylation of EGFRP (epidermal growth factor receptor peptide, a 21 mer) in the presence of ^{33}P-ATP. Compounds were tested in 10 fold serial dilutions over the range of 100μM to 0.001μM in 1% DMSO. Each concentration of inhibitor was tested in triplicate. Compounds were evaluated in 50μl reaction volumes in the presence of 25 mM Hepes pH 7.5, 10 mM magnesium acetate, 4% glycerol, 0.4% bovine serum albumin, 0.4mM DTT, 50μM unlabeled ATP, 25 μg EGFRP (200μM), and 0.05 uCi gamma ^{33}P-ATP. Reactions were initiated by addition of 0.09 μg of activated, purified human GST-p38 kinase alpha. Activation was carried out using GST-MKK6 (5:1,p38:MKK6) for one hour at 30 °C in the presence of 50μM ATP. Following incubation for 60 minutes at room temperature, the reaction was stopped by addition of 150μl of AG 1X8 resin in 900 mM sodium formate buffer, pH 3.0 (1 volume resin to 2 volumes buffer). The mixture was mixed three times with pipetting and the resin was allowed to settle. A total of 50μl of clarified solution head volume was transferred from the reaction wells to Microlite-2 plates. 150μl of Microscint 40 was then added to each well of the Microlite plate, and the plate was sealed, mixed, and counted.

TABLE I

Example	p38 kinase[1] IC50 μM	p38 kinase[2] IC50 μM
1	8.7	0.66
2	1.0	2.8

[1] p38α in vitro assay results based on PHAS-I assay procedure

[2] p38α in vitro assay results based on EGFRP assay procedure

TNF Cell Assays

Method of Isolation of Human Peripheral Blood Mononuclear Cells:

Human whole blood was collected in Vacutainer tubes containing EDTA as an anticoagulant. A blood sample (7 ml) was carefully layered over 5 ml PMN Cell Isolation Medium (Robbins Scientific) in a 15 ml round bottom centrifuge tube. The sample was centrifuged at 450-500 x g for 30-35 minutes in a swing out rotor at room temperature. After centrifugation, the top band of cells were removed and washed 3 times with PBS w/o calcium or magnesium. The cells were centrifuged at 400 x g for 10 minutes at room temperature. The cells were resuspended in Macrophage Serum Free Medium (Gibco BRL) at a concentration of 2 million cells/ml.

LPS Stimulation of Human PBMs:

PBM cells (0.1 ml, 2 million/ ml) were co-incubated with 0.1 ml compound (10-0.41 μM, final concentration) for 1 hour in flat bottom 96 well microtiter plates. Compounds were dissolved in DMSO initially and diluted in TCM for a final

concentration of 0.1% DMSO. LPS (Calbiochem, 20 ng/ml, final concentration) was then added at a volume of 0.010 ml. Cultures were incubated overnight at 37 °C. Supernatants were then removed and tested by ELISA for TNF-a and IL1-b. Viability was analyzed using MTS. After 0.1 ml supernatant was collected, 0.020 ml MTS was added to remaining 0.1 ml cells. The cells were incubated at 37 °C for 2-4 hours, then the O.D. was measured at 490-650 nM.

Maintenance and Differentiation of the U937 Human Histiocytic Lymphoma Cell Line:

U937 cells (ATCC) were propagated in RPMI 1640 containing 10% fetal bovine serum, 100 IU/ml penicillin, 100 μg/ml streptomycin, and 2 mM glutamine (Gibco). Fifty million cells in 100 ml media were induced to terminal monocytic differentiation by 24 hour incubation with 20 ng/ml phorbol 12-myristate 13-acetate (Sigma). The cells were washed by centrifugation (200 x g for 5 min) and resuspended in 100 ml fresh medium. After 24-48 hours, the cells were harvested, centrifuged, and resuspended in culture medium at 2 million cells/ml.

LPS Stimulation of TNF production by U937 Cells:

U937 cells (0.1 ml, 2 million/ml) were incubated with 0.1 ml compound (0.004-50 μM, final concentration) for 1 hour in 96 well microtiter plates. Compounds were prepared as 10 mM stock solutions in DMSO and diluted in culture medium to yield a final DMSO concentration of 0.1% in the cell assay. LPS (E coli, 100 ng/ml final concentration) was then added at a volume of 0.02 ml. After 4 hour incubation at 37°C, the amount of TNF-α released in the culture medium was quantitated by ELISA.

Inhibitory potency is expressed as IC50 (μM). Results are shown in Table II.

TABLE II

Example	TNF Cell IC50 μM
1	0.6
2	2.3

Rat Assay

The efficacy of the novel compounds in blocking the production of TNF also was evaluated using a model based on rats challenged with LPS. Male Harlen Lewis rats [Sprague Dawley Co.] were used in this model. Each rat weighed approximately 300 g and was fasted overnight prior to testing. Compound administration was typically by oral gavage (although intraperitoneal, subcutaneous and intravenous administration were also used in a few instances) 1 to 24 hours prior to the LPS challenge. Rats were administered 30 μg/kg LPS [salmonella typhosa, Sigma Co.] intravenously via the tail vein. Blood was collected via heart puncture 1 hour after the LPS challenge. Serum samples were stored at -20 °C until quantitative analysis of TNF-α by Enzyme Linked-Immuno-Sorbent Assay ("ELISA") [Biosource]. Additional details of the assay are set forth in Perretti, M., et al., Br. J. Pharmacol. (1993), 110, 868-874, which is incorporated by reference in this application.

Mouse Assay

Mouse Model Of LPS-Induced TNF Alpha Production:

TNF alpha was induced in 10-12 week old BALB/c female mice by tail vein injection with 100 ng lipopolysaccharide (from S. Typhosa) in 0.2 ml saline. One hour later mice were bled from the retroorbital sinus and TNF concentrations in serum from clotted blood were quantified by ELISA. Typically, peak levels of serum TNF ranged from 2-6 ng/ml one hour after LPS injection.

The compounds tested were administered to fasted mice by oral gavage as a suspension in 0.2 ml of 0.5% methylcellulose and 0.025% Tween 20 in water at 1 hour or 6 hours prior to LPS injection. The 1 hour protocol allowed evaluation of compound potency at Cmax plasma levels whereas the 6 hour protocol allowed estimation of compound duration of action. Efficacy was determined at each time point as percent inhibition of serum TNF levels relative to LPS injected mice that received vehicle only.

Induction And Assessment Of Collagen-Induced Arthritis In Mice:

Arthritis was induced in mice according to the procedure set forth in J.M. Stuart, Collagen Autoimmune Arthritis, Annual Rev. Immunol. 2:199 (1984), which is incorporated herein by reference. Specifically, arthritis was induced in 8-12 week old DBA/1 male mice by injection of 50 μg of chick type II collagen (CII) (provided by Dr. Marie Griffiths, Univ. of Utah, Salt Lake City, UT) in complete Freund's adjuvant (Sigma) on day 0 at the base of the tail. Injection volume was 100 μl. Animals were boosted on day 21 with 50 μg of CII in incomplete Freund's adjuvant (100 μl volume). Animals were

evaluated several times each week for signs of arthritis. Any animal with paw redness or swelling was counted as arthritic. Scoring of arthritic paws was conducted in accordance with the procedure set forth in Wooley et al., Genetic Control of Type II Collagen Induced Arthritis in Mice: Factors Influencing Disease Suspectibility and Evidence for Multiple MHC Associated Gene Control., Trans. Proc., 15:180 (1983). Scoring of severity was carried out using a score of 1-3 for each paw (maximal score of 12/mouse). Animals displaying any redness or swelling of digits or the paw were scored as 1. Gross swelling of the whole paw or deformity was scored as 2. Ankylosis of joints was scored as 3. Animals were evaluated for 8 weeks. 8-10 animals per group were used.

Preparation And Administration Of Compounds:

The compounds tested on mice having collagen-induced arthritis were prepared as a suspension in 0.5% methylcelluose (Sigma, St. Louis, MO), 0.025% Tween 20 (Sigma). The compound suspensions were administered by oral gavage in a volume of 0.1 ml b.i.d. Administration began on day 20 post collagen injection and continued daily until final evaluation on day 56. Scoring of arthritic paws was conducted as set forth above.

Also embraced within this invention is a class of pharmaceutical compositions comprising the active compounds of this invention in association with one or more non-toxic, pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The active compounds of the present invention may be administered by any suitable route,

preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The active compounds and composition may, for example, be administered orally, intravascularly (IV), intraperitoneally, subcutaneously, intramuscularly (IM) or topically. For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, hard or soft capsule, lozenges, dispensable powders, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. The active ingredient may also be administered by injection (IV, IM, subcutaneous or jet) as a composition wherein, for example, saline, dextrose, or water may be used as a suitable carrier. The pH of the composition may be adjusted, if necessary, with suitable acid, base, or buffer. Suitable bulking, dispersing, wetting or suspending agents, including mannitol and PEG 400, may also be included in the composition. A suitable parenteral composition can also include a compound formulated as a sterile solid substance, including lyophilized powder, in injection vials. Aqueous solution can be added to dissolve the compound prior to injection. The amount of therapeutically active compounds that are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the inflammation or inflammation related disorder, the route and frequency of administration, and the particular compound employed, and thus may vary

widely. The pharmaceutical compositions may contain active ingredients in the range of about 0.1 to 1000 mg, preferably in the range of about 7.0 to 350 mg. A daily dose of about 0.01 to 100 mg/kg body weight, preferably between about 0.1 and about 50 mg/kg body weight and most preferably between about 0.5 to 30 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day. In the case of skin conditions, it may be preferable to apply a topical preparation of compounds of this invention to the affected area two to four times a day. For disorders of the eye or other external tissues, e.g., mouth and skin, the formulations are preferably applied as a topical gel, spray, ointment or cream, or as a suppository, containing the active ingredients in a total amount of, for example, 0.075 to 30% w/w, preferably 0.2 to 20% w/w and most preferably 0.4 to 15% w/w. When formulated in an ointment, the active ingredients may be employed with either paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example at least 30% w/w of a polyhydric alcohol such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol, polyethylene glycol and mixtures thereof. The topical formulation may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogs. The compounds of this invention can also be administered by a transdermal device. Preferably topical administration will be accomplished using a patch

either of the reservoir and porous membrane type or of a solid matrix variety. In either case, the active agent is delivered continuously from the reservoir or microcapsules through a membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the recipient. In the case of microcapsules, the encapsulating agent may also function as the membrane. The transdermal patch may include the compound in a suitable solvent system with an adhesive system, such as an acrylic emulsion, and a polyester patch. The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glycerol monostearate, and sodium lauryl sulfate, among others. The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in

pharmaceutical emulsion formulations is very low. Thus, the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters may be used. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used. Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredients are dissolved or suspended in suitable carrier, especially an aqueous solvent for the active ingredients. The anti-inflammatory active ingredients are preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% and particularly about 1.5% w/w. For therapeutic purposes, the active compounds of this combination invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered *per os*, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain

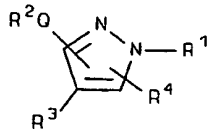
a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

All patent documents listed herein are incorporated by reference.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations.

WHAT WE CLAIM IS:

1. A compound of Formula I

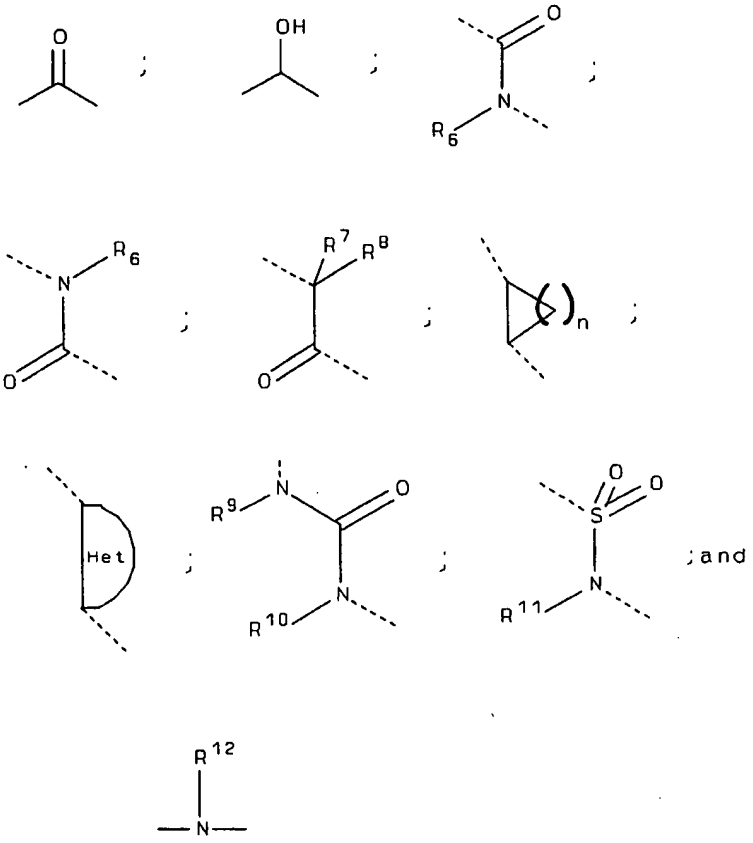


(I)

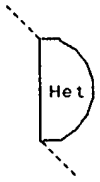
wherein

R^1 is selected from hydrido, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heterocyclyl, cycloalkylalkylene, cycloalkenylalkylene, haloalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, aralkyl, aralkenyl, aralkynyl, heterocyclylalkylene, alkoxyalkyl, aryloxyalkyl, heterocyclyloxyalkyl, mercaptoalkyl, mercaptoaryl, mercaptoheterocyclyl, alkylthioalkylene, arylthioalkylene, amino, alkylamino, arylamino, aminoalkyl, aminoaryl, alkylaminoalkylene, and heterocyclylalkylene; and

Q is selected from oxy, thio, alkylene, alkenylene, alkynylene, sulfinyl, sulfonyl,



wherein



represents a four to eight membered ring heterocyclylidenyl comprising one or more heteroatoms selected from oxygen, sulfur and nitrogen; and

wherein n is an integer from 1 to 7; and

R^2 is aryl optionally substituted with one or more radicals independently selected from halo, alkyl, alkenyl, alkynyl, aryl, heterocyclyl, alkoxy, alkenoxy, alkynoxy, aryloxy, heterocyclyloxy, aralkoxy, alkylthio, arylthio, alkylsulfinyl, arylsulfinyl, alkylsulfonyl, arylsulfonyl, amino, alkylamino, alkenylamino,

alkynylamino, arylamino, heterocyclylamino, aminoalkyl, aminocarbonyl, cyano, hydroxyl, hydroxyalkyl, alkoxycarbonyl, aryloxycarbonyl, heterocyclyloxycarbonyl, formyl, nitro, nitroalkyl, alkylcarbonylamino, arylcarbonylamino, haloalkylsulfinyl, haloalkylsulfonyl, alkylcarbonyl, arylcarbonyl, heterocyclylcarbonyl, and haloalkyl; and

R^3 is heteroaryl optionally substituted with one or more radicals independently selected from halo, alkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, amino, aminocarbonyl, cyano, hydroxyl, alkoxycarbonyl, formyl, aralkyl, aralkyloxy, aralkylthio, aralkylamino, aminosulfonyl, alkylamino, nitro, arylamino, alkylcarbonylamino, halosulfonyl, aminoalkyl, haloalkyl and alkylcarbonyl; and

R^4 is selected from hydrido, alkyl, aryl, haloalkyl, heterocyclyl, cycloalkyl, alkenyl, cycloalkenyl, alkoxy, alkylthio, arylthio, carboxy, alkoxycarbonyl, carboxyalkyl, alkoxycarbonylalkylene, heterocyclylalkyl, amino, alkylamino, alkynylamino, arylamino, heterocyclylamino, heterocyclylalkylamino, heterocyclylaminoalkyl, and aminoheterocyclylamino; wherein the aryl, heterocyclyl, cycloalkyl, cycloalkenyl groups are optionally substituted with one or more radicals independently selected from halo, amino, alkyl, alkenyl, alkynyl, alkoxy, aryloxy, aralkoxy, haloalkyl, and alkylamino; and wherein the amino radicals of the heterocylcylalkylamino and heterocylcylaminoalkyl group are optionally substituted with one or more alkyl; and

R^6 is selected from hydrido, alkyl, alkenyl, and alkynyl; and

R^7 and R^8 are independently selected from hydrido, alkyl, alkenyl, and alkynyl, or together form a carbocyclic or heterocyclic ring having three to eight members; and

R^9 is selected from hydrido, alkyl, alkenyl, and alkynyl; and

R^{10} is selected from hydrido, alkyl, alkenyl, and alkynyl; and

R^{11} is selected from hydrido, alkyl, alkenyl, and alkynyl; and

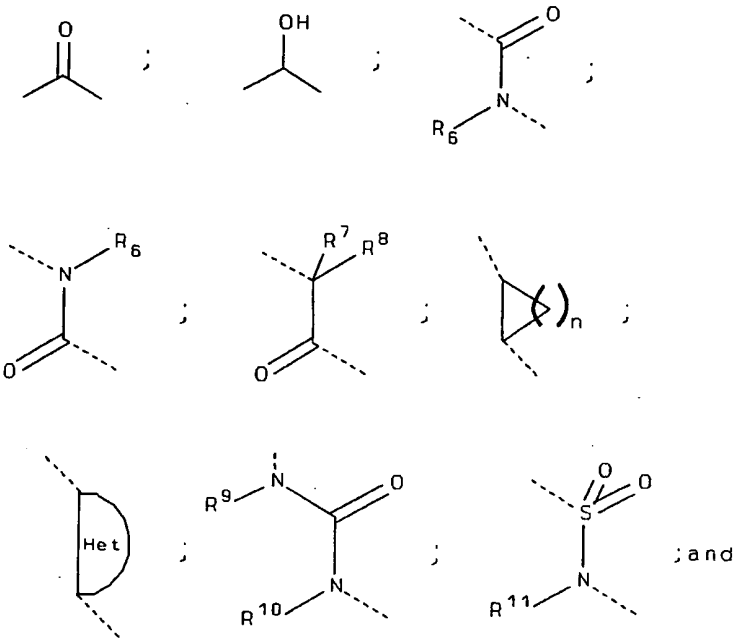
R^{12} is selected from hydrido and alkyl; or

a pharmaceutically-acceptable salt or tautomer thereof.

2. Compound of Claim 1 wherein

R^1 is selected from hydrido, lower alkyl, lower alkynyl, lower cycloalkylalkylene, lower haloalkyl, lower hydroxyalkyl, lower alkoxyalkyl, lower thioalkyl, lower alkylthioalkylene, amino, lower alkylamino, lower arylamino, lower alkylaminoalkylene, and lower heterocyclylalkylene; and

Q is selected from lower alkylene, lower alkenylene, sulfinyl, sulfonyl,



wherein



represents a four to eight membered ring heterocyclylidenyl comprising one or more heteroatoms selected from oxygen, sulfur and nitrogen; and

wherein n is an integer from 1 to 7; and

R^2 is aryl optionally substituted with one or more radicals independently selected from halo, lower alkyl, lower alkoxy, lower aryloxy, lower aralkoxy, amino, hydroxyl, nitro, cyano, lower haloalkyl, lower alkylamino, and lower alkynylamino; and

R^3 is selected from 5- to 10-membered heterocyclyl optionally substituted with one or more radicals independently selected from lower alkylthio, lower alkylsulfonyl, aminosulfonyl, halo, lower alkyl, lower alkylsulfinyl, cyano, lower alkoxycarbonyl, aminocarbonyl, formyl, lower aralkyl, lower aralkyloxy, lower aralkylthio, lower aralkylamino, lower alkylcarbonylamino, lower haloalkyl, hydroxyl, lower alkoxy, amino, lower alkylamino, lower aminoalkyl, phenylamino, nitro, halosulfonyl and lower alkylcarbonyl; and

R^4 is selected from hydrido, lower alkyl, aryl, lower haloalkyl, 5-10 membered heterocyclyl, lower alkylamino, lower alkynylamino, phenylamino, lower cycloalkyl, lower alkenyl, lower cycloalkenyl, lower alkoxy, lower alkylthio, carboxy, lower alkoxycarbonyl, lower carboxyalkyl, lower alkoxycarbonylalkylene, lower heterocyclylalkyl, lower heterocylcylalkylamino, and lower heterocylcylaminoalkyl; wherein the aryl, 5-10 membered heteroaryl, lower cycloalkyl and lower cycloalkenyl groups are optionally substituted with one or more radicals independently selected from halo, lower alkyl, lower alkenyl, lower alkynyl, alkoxy, phenoxy, lower aralkoxy, lower haloalkyl, and lower alkylamino; and wherein the amino radicals of the lower heterocylcylalkylamino and lower heterocylcylaminoalkyl group are optionally substituted with one or more lower alkyl; and

R^6 is selected from hydrido, lower alkyl, lower alkenyl, and lower alkynyl; and

R^7 and R^8 are independently selected from hydrido, lower lower alkyl, lower alkenyl, and lower alkynyl, or together form a carbocyclic or heterocyclic ring having three to eight members; and

R^9 is selected from hydrido, lower alkyl, lower alkenyl, and lower alkynyl; and

R^{10} is selected from hydrido, lower alkyl, lower alkenyl, and lower alkynyl; and

R^{11} is selected from hydrido, lower alkyl, lower alkenyl, and lower alkynyl; and

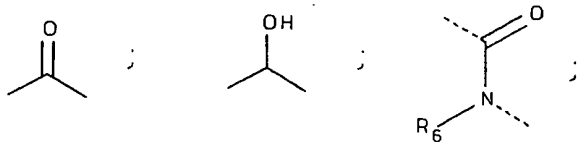
R^{12} is selected from hydrido and lower alkyl; or

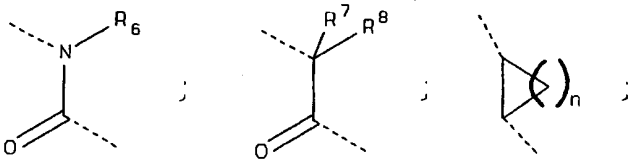
a pharmaceutically-acceptable salt or tautomer thereof.

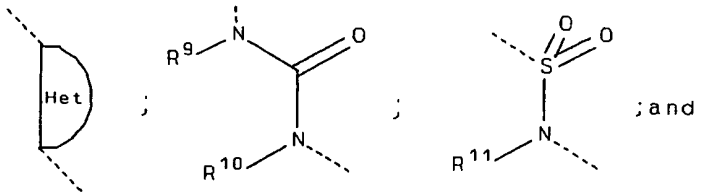
3. Compound of Claim 2 wherein

R^1 is selected from hydrido, lower alkyl, lower alkynyl, lower cycloalkylalkylene, lower haloalkyl, lower hydroxyalkyl, lower alkoxyalkyl, lower thioalkyl, lower alkylthioalkylene, lower alkylaminoalkylene, and lower heterocyclylalkylene; and

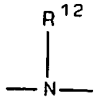
Q is selected from lower alkylene, lower alkenylene,



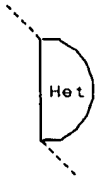




;and



wherein



represents a four to eight membered ring heterocyclylidenyl comprising one or more heteroatoms selected from oxygen, sulfur and nitrogen; and

wherein n is an integer from 1 to 7; and

R^2 is aryl optionally substituted with one or more radicals independently selected from halo, lower alkyl, lower alkoxy, lower aryloxy, lower aralkoxy, amino, hydroxyl, nitro, cyano, lower haloalkyl, lower alkylamino, and lower alkynylamino; and

R^3 is 6-membered heteroaryl optionally substituted with one or more radicals independently selected from halo, lower alkyl, cyano, phenethyl, benzyl, benzyloxy, benzylthio, benzylamino, phenethylamino, aminocarbonyl, lower alkylcarbonylamino, hydroxyl, amino, lower alkylamino, lower aminoalkyl, and phenylamino; and

R^4 is selected from hydrido, lower alkyl, phenyl, lower haloalkyl, 5-10 membered heterocyclyl, lower alkylamino, lower alkynylamino, phenylamino, lower cycloalkyl, lower alkenyl, lower cycloalkenyl, lower alkoxy, lower heterocyclylaminoalkyl, and lower heterocyclylalkylamino; wherein the phenyl, 5-10 membered heteroaryl, lower cycloalkyl and lower cycloalkenyl groups are optionally substituted with one or more radicals independently selected from halo, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, phenoxy, lower aralkoxy, lower haloalkyl, amino, hydroxyl, cyano and lower alkylamino; and wherein the amino radicals of lower heterocyclyl alkylamino and lower heterocyclylaminoalkyl are optionally substituted with one or more lower alkyl; and

R^6 is selected from hydrido, lower alkyl, lower alkenyl, and lower alkynyl; and

R^7 and R^8 are independently selected from hydrido, lower lower alkyl, lower alkenyl, and lower alkynyl, or together form a carbocyclic or heterocyclic ring having three to eight members; and

R^9 is selected from hydrido, lower alkyl, lower alkenyl, and lower alkynyl; and

R^{10} is selected from hydrido, lower alkyl, lower alkenyl, and lower alkynyl; and

R^{11} is selected from hydrido, lower alkyl, lower alkenyl, and lower alkynyl; and

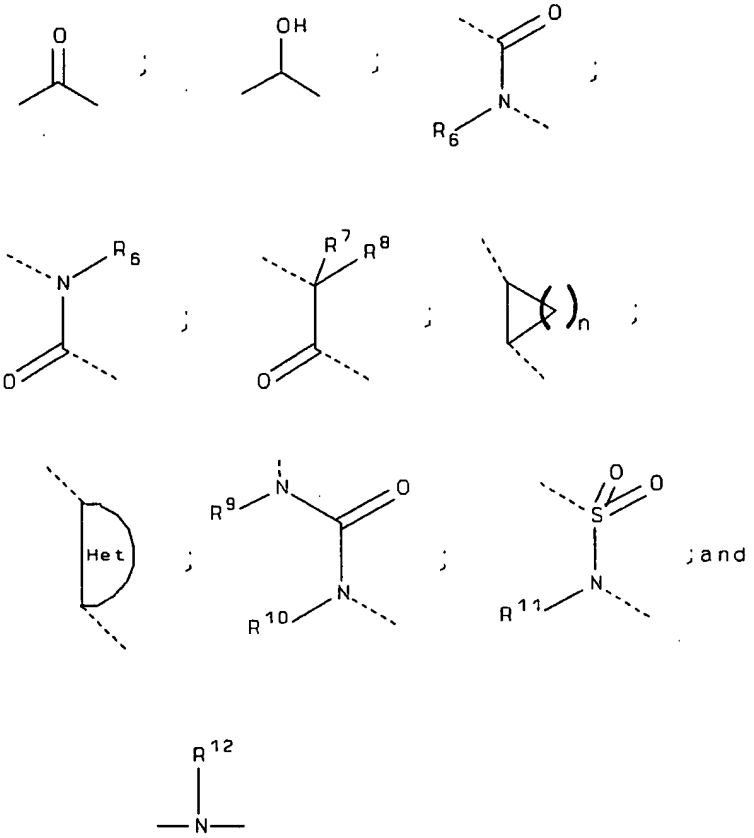
R^{12} is selected from hydrido and lower alkyl; or

a pharmaceutically-acceptable salt or tautomer thereof.

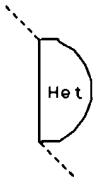
4. Compounds of Claim 3 wherein

R^1 is selected from hydrido, methyl, ethyl, propyl, isopropyl, tert-butyl, isobutyl, ethynyl, propargyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloroethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, morpholinomethyl, pyrrolidinylmethyl, piperazinylmethyl, piperidinylmethyl, pyridylmethyl, thienylmethyl, methoxymethyl, ethoxymethyl, methylaminomethyl, cyclohexylmethyl, hydroxymethyl, hydroxylethyl, thiomethyl, and methylthiomethyl; and

Q is selected from methylene, ethylene, propylene, ethenylene, propenylenyl



wherein



represents a four to eight membered ring heterocyclylidenyl comprising one or more heteroatoms selected from oxygen, sulfur and nitrogen; and

wherein n is an integer from 1 to 7; and

R^2 is phenyl optionally substituted with one or more radicals independently selected from fluoro, chloro, bromo, methyl, ethyl, isopropyl, tert-butyl, isobutyl, methoxy, ethoxy, phenoxy, benzyloxy, trifluoromethyl, fluoromethyl, difluoromethyl, amino, cyano, nitro,

dimethylamino, ethynylamino, propargylamino, and hydroxyl; and

R^3 is selected from pyridyl, pyridium, and pyrimidyl; wherein R^3 is optionally substituted with one or more radicals independently selected from fluoro, chloro, bromo, methyl, ethyl, isopropyl, cyano, aminocarbonyl, methylcarbonylamino, hydroxy, benzyl, phenethyl, methylamino, ethylamino, dimethylamino, diethylamino, aminomethyl, aminoethyl, N-methyl-N-phenylamino, phenylamino, diphenylamino, benzylamino, phenethylamino, and amino; and

R^4 is selected from hydrido, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, isobutyl, phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, pyridyl, thienyl, isothiazolyl, isoxazolyl, thiazolyl, oxazolyl, pyrimidinyl, quinolyl, isoquinolinyl, imidazolyl, benzimidazolyl, furyl, benzofuryl, methoxy, ethoxy, trifluoromethyl, fluoromethyl, methylamino, ethynylamino, propargylamino, piperidinyl, piperazinyl, piperadinylmethyl, piperadinylmethylamino, piperadinylaminomethyl, piperazinylmethyl, piperazinylmethylamino, piperazinylaminomethyl; wherein the phenyl piperadinyl and piperazinyl groups are optionally substituted with one or more radicals independently selected from fluoro, chloro, bromo, methyl, ethyl, isopropyl, tert-butyl, isobutyl, propargyl, methoxy, ethoxy, phenoxy, benzyloxy, trifluoromethyl, fluoromethyl, difluoromethyl, amino, hydroxyl, cyano and dimethylamino; and wherein the amino radicals of piperadinylmethylamino, piperadinylaminomethyl, piperazinylmethylamino, and piperazinylaminomethyl are optionally substituted with one or more methyl; and

R^6 is selected from hydrido, methyl, ethyl, propyl, isopropyl, tert-butyl, and isobutyl; and

R^7 and R^8 are independently selected from hydrido, methyl, ethyl, propyl, isopropyl, tert-butyl, and isobutyl, or together form a carbocyclic or heterocyclic ring having three to eight members; and

R^9 is selected from hydrido, methyl, ethyl, propyl, isopropyl, tert-butyl, and isobutyl; and

R^{10} is selected from hydrido, methyl, ethyl, propyl, isopropyl, tert-butyl, and isobutyl; and

R^{11} is selected from hydrido, methyl, ethyl, propyl, isopropyl, tert-butyl, and isobutyl; and

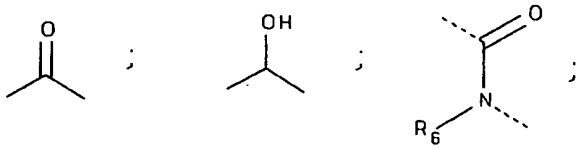
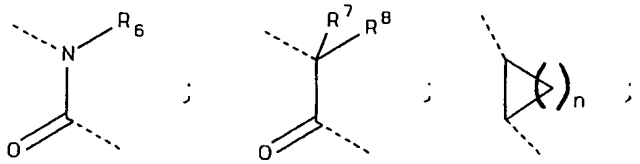
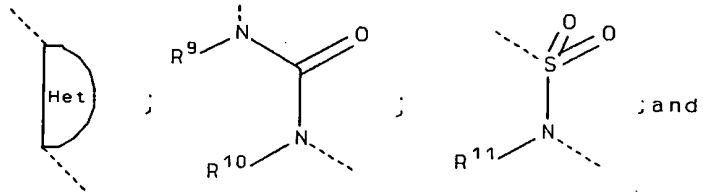
R^{12} is selected from hydrido, methyl, ethyl, propyl, isopropyl, tert-butyl, and isobutyl; or

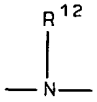
a pharmaceutically-acceptable salt or tautomer thereof.

5. Compound of Claim 4 wherein

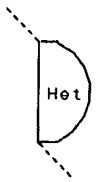
R^1 is hydrido or methyl; and

Q is selected from methylene, ethylene, ethenylene,



wherein



represents a four to eight membered ring heterocyclylidenyl comprising one or more heteroatoms selected from oxygen, sulfur and nitrogen; and

wherein n is an integer from 1 to 3; and

R^2 is phenyl optionally substituted with one or more radicals independently selected from fluoro, chloro, bromo, methyl, ethyl, isopropyl, tert-butyl, isobutyl, methoxy, ethoxy, phenoxy, benzyloxy, trifluoromethyl, fluoromethyl, difluoromethyl, amino, cyano, nitro, dimethylamino, and hydroxyl; and

R^3 is pyridyl optionally substituted with one or more radicals independently selected from fluoro, chloro, bromo, methyl, cyano, benzyl, phenethyl, aminocarbonyl, hydroxyl, dimethylamino, benzylamino, phenethylamino, aminomethyl and amino; and

R^4 is selected from hydrido, methyl, ethyl, propyl, propargylamino, and phenyl optionally substituted with one or more radicals independently selected from fluoro, chloro, bromo, methyl, ethyl, isopropyl, methoxy, ethoxy, phenoxy, benzyloxy, trifluoromethyl, dimethylamino, ethynylamino and propargylamino; and

R^6 is selected from hydrido and methyl; and

R^7 and R^8 are independently selected from hydrido and methyl; and

R^9 is selected from hydrido and methyl; and

R^{10} is selected from hydrido and methyl; and

R^{11} is selected from hydrido and methyl; and

R^{12} is selected from hydrido and methyl; or

a pharmaceutically-acceptable salt or tautomer thereof.

6. Compound of Claim 1 selected from compounds, their tautomers and their pharmaceutically acceptable salts, of the group consisting of

4-[3-methyl-5-(2-phenylethenyl)-1H-pyrazol-4-yl]pyridine;

4-[3-methyl-5-(2-phenylethyl)-1H-pyrazol-4-yl]pyridine;

4-[3-methyl-5-[2-(3-fluorophenyl)ethyl]-1H-pyrazol-4-yl]pyridine;

4-[3-[2-(3-fluorophenyl)ethyl]-1H-pyrazol-4-yl]pyridine;

4-[1-methyl-3-[2-(3-fluorophenyl)ethyl]-1H-pyrazol-4-yl]pyridine;

4-[3-[2-(4-chlorophenyl)ethyl]-1H-pyrazol-4-yl]pyridine;

4-[1-methyl-3-[2-(4-chlorophenyl)ethyl]-1H-pyrazol-4-yl]pyridine;

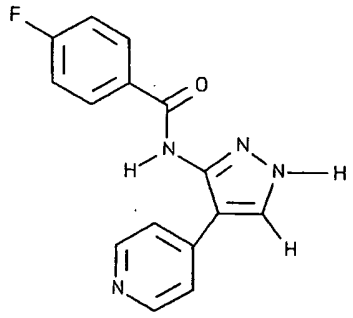
3-methyl-4-[1-methyl-3-[2-(4-chlorophenyl)ethyl]-1H-pyrazol-4-yl]pyridine;

4-[3-[2-(3-chlorophenyl)ethyl]-1H-pyrazol-4-yl]pyridine;
3-methyl-4-[1-methyl-3-[2-(3,4-dichlorophenyl)ethyl]-1H-pyrazol-4-yl]pyridine;
3-methyl-4-[1-methyl-3-[2-(4-chlorophenyl)ethyl]-1H-pyrazol-4-yl]pyridine;
4-[3-methyl-5-[2-(3-fluorophenyl)ethenyl]-1H-pyrazol-4-yl]pyridine;
4-[3-[2-(3-fluorophenyl)ethenyl]-1H-pyrazol-4-yl]pyridine;
4-[1-methyl-3-[2-(3-fluorophenyl)ethenyl]-1H-pyrazol-4-yl]pyridine;
4-[3-[2-(4-chlorophenyl)ethenyl]-1H-pyrazol-4-yl]pyridine;
4-[1-methyl-3-[2-(4-chlorophenyl)ethenyl]-1H-pyrazol-4-yl]pyridine;
3-methyl-4-[1-methyl-3-[2-(4-chlorophenyl)ethenyl]-1H-pyrazol-4-yl]pyridine;
4-[3-[2-(3-chlorophenyl)ethenyl]-1H-pyrazol-4-yl]pyridine;
3-methyl-4-[1-methyl-3-[2-(3,4-dichlorophenyl)ethenyl]-1H-pyrazol-4-yl]pyridine;
3-methyl-4-[1-methyl-3-[2-(4-chlorophenyl)ethenyl]-1H-pyrazol-4-yl]pyridine;
4-[3-methyl-5-(3-fluorobenzyl)-1H-pyrazol-4-yl]pyridine;
4-[3-(3-fluorobenzyl)-1H-pyrazol-4-yl]pyridine;
4-[1-methyl-3-(3-fluorobenzyl)-1H-pyrazol-4-yl]pyridine;
4-[3-benzyl-1H-pyrazol-4-yl]pyridine;
4-[3-(4-chlorobenzyl)-1H-pyrazol-4-yl]pyridine;
4-[1-methyl-3-(4-chlorobenzyl)-1H-pyrazol-4-yl]pyridine;
3-methyl-4-[1-methyl-3-(4-chlorobenzyl)-1H-pyrazol-4-yl]pyridine;
4-[3-(3-chlorobenzyl)-1H-pyrazol-4-yl]pyridine;
3-methyl-4-[1-methyl-3-(3,4-dichlorobenzyl)-1H-pyrazol-4-yl]pyridine;
3-methyl-4-[1-methyl-3-(4-chlorobenzyl)-1H-pyrazol-4-yl]pyridine;

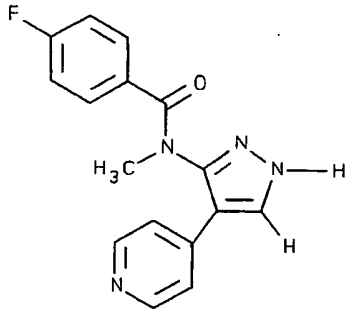
(3-fluorophenyl)[3-methyl-4-(4-pyridinyl)-1H-pyrazol-5-yl]methanone;
(3-fluorophenyl)[4-(4-pyridinyl)-1H-pyrazol-3-yl]methanone;
(3-fluorophenyl)[1-methyl-4-(4-pyridinyl)-1H-pyrazol-3-yl]methanone;
phenyl[1-methyl-4-(4-pyridinyl)-1H-pyrazol-3-yl]methanone;
(4-chlorophenyl)[4-(4-pyridinyl)-1H-pyrazol-3-yl]methanone;
(4-chlorophenyl)[1-methyl-4-(4-pyridinyl)-1H-pyrazol-3-yl]methanone;
(4-chlorophenyl)[1-methyl-4-(3-methyl-4-pyridinyl)-1H-pyrazol-3-yl]methanone;
(3-chlorophenyl)[4-(4-pyridinyl)-1H-pyrazol-3-yl]methanone;
(3,4-dichlorophenyl)[1-methyl-4-(3-methyl-4-pyridinyl)-1H-pyrazol-3-yl]methanone;
(4-chlorophenyl)[1-methyl-4-(3-methyl-4-pyridinyl)-1H-pyrazol-3-yl]methanone;
α-(3-fluorophenyl)-3-methyl-4-(4-pyridinyl)-1H-pyrazole-5-methanol;
α-(3-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazole-3-methanol;
α-(3-fluorophenyl)-1-methyl-4-(4-pyridinyl)-1H-pyrazole-3-methanol;
α-phenyl-1-methyl-4-(4-pyridinyl)-1H-pyrazole-3-methanol;
α-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazole-3-methanol;
α-(4-chlorophenyl)-1-methyl-4-(4-pyridinyl)-1H-pyrazole-3-methanol;
α-(4-chlorophenyl)-1-methyl-4-(3-methyl-4-pyridinyl)-1H-pyrazole-3-methanol;
α-(3-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazole-3-methanol;

α-(3,4-dichlorophenyl)-1-methyl-4-(3-methyl-4-pyridinyl)-1H-pyrazole-3-methanol;
α-(4-chlorophenyl)-1-methyl-4-(3-methyl-4-pyridinyl)-1H-pyrazole-3-methanol; and
4-[5-(2-phenylethyl)-1H-pyrazol-4-yl]pyridine.

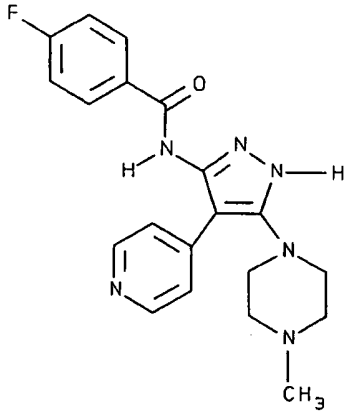
7. Compound of Claim 1 selected from compounds, their tautomers and their pharmaceutically acceptable salts, of the group consisting of



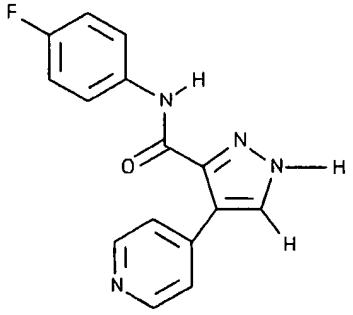
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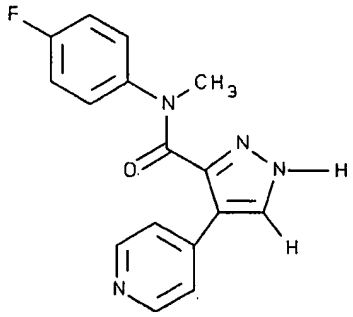


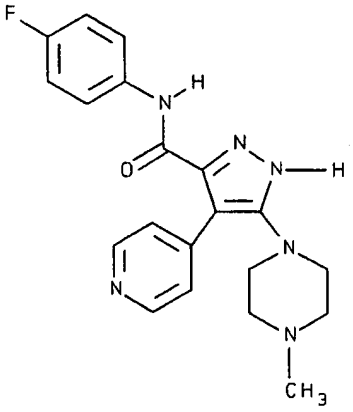
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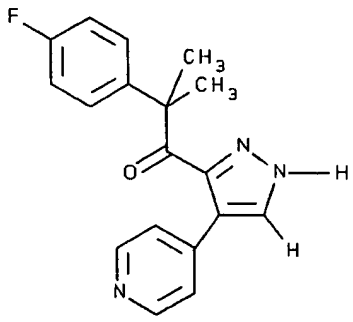


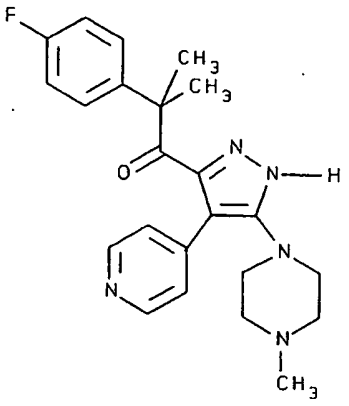
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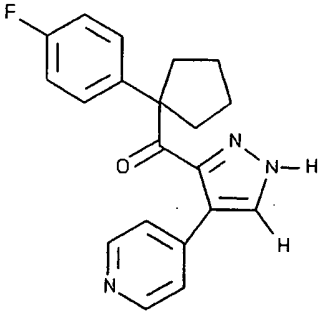

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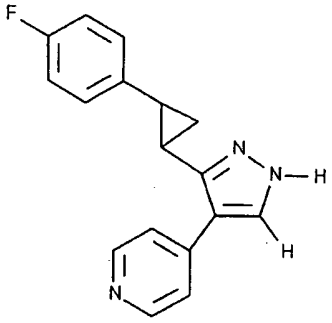

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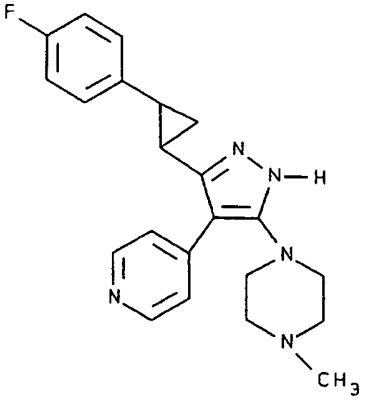
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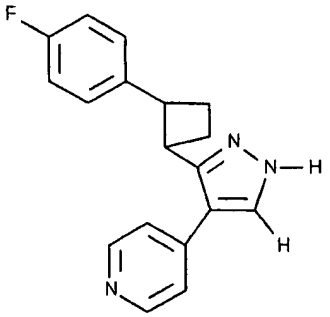
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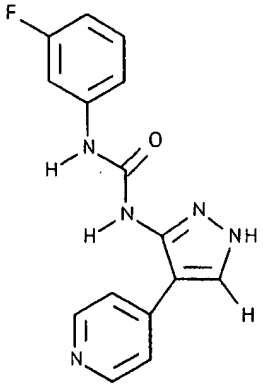
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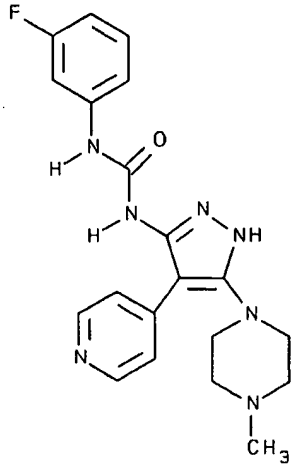
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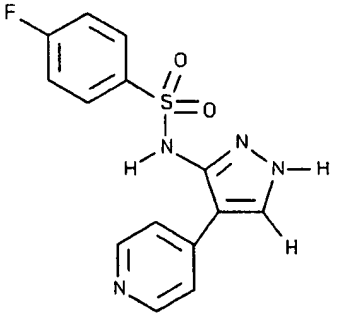
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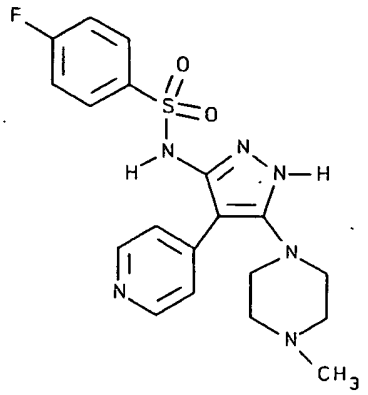
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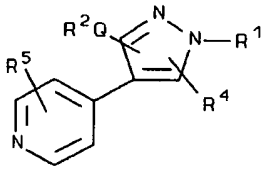
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; and



8. A compound of Formula II

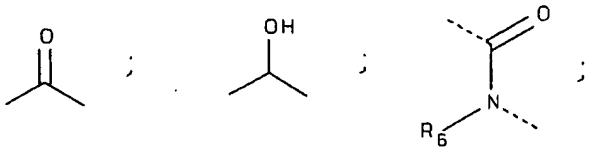
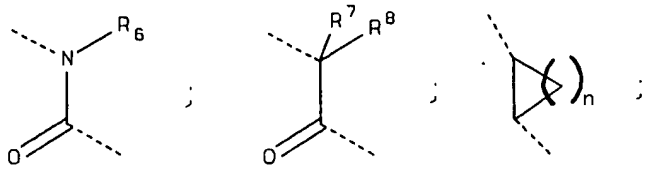
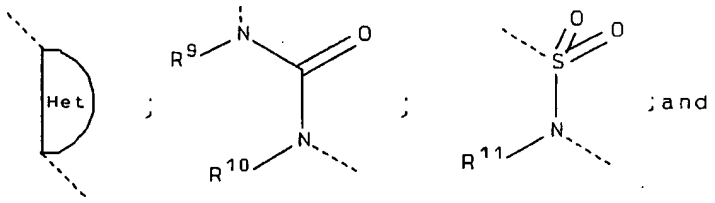
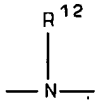


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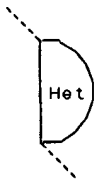
wherein

R^1 is selected from hydrido and lower alkyl; and

Q is selected from lower alkylene, lower alkenylene,

wherein



represents a four to eight membered ring heterocyclylidenyl comprising one or more heteroatoms selected from oxygen, sulfur and nitrogen; and

wherein n is an integer from 1 to 4; and

R^2 is phenyl optionally substituted with one or more radicals independently selected from halo and lower alkyl; and

R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are independently selected from hydrido and lower alkyl; or

a pharmaceutically-acceptable salt or tautomer thereof.

9. Compound of Claim 8 wherein

R^1 is selected from hydrido and methyl; and

wherein Q is selected from methylene, ethylene, ethenylene,  and ;

R^2 is phenyl optionally substituted with one or more radicals independently selected from fluoro, chloro and bromo; and

R^4 is selected from hydrido, methyl and ethyl; and

R^5 is selected from hydrido and methyl; or

a pharmaceutically-acceptable salt or tautomer thereof.

10. Compound of Claim 9 selected from compounds, their tautomers and their pharmaceutically acceptable salts, of the group consisting of

4-[3-methyl-5-(2-phenylethenyl)-1H-pyrazol-4-yl]pyridine;

4-[3-methyl-5-(2-phenylethyl)-1H-pyrazol-4-yl]pyridine; and

4-[5-(2-phenylethyl)-1H-pyrazol-4-yl]pyridine.

11. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Claim 1; or a pharmaceutically-acceptable salt thereof.

12. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Claim 2; or a pharmaceutically-acceptable salt thereof.

13. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Claim 3; or a pharmaceutically-acceptable salt thereof.

14. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Claim 4; or a pharmaceutically-acceptable salt thereof.

15. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Claim 5; or a pharmaceutically-acceptable salt thereof.

16. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Claim 6; or a pharmaceutically-acceptable salt thereof.

17. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Claim 7; or a pharmaceutically-acceptable salt thereof.

18. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Claim 8; or a pharmaceutically-acceptable salt thereof.

19. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Claim 9; or a pharmaceutically-acceptable salt or tautomer thereof.

20. A method of treating a TNF mediated disorder, said method comprising treating the subject having or susceptible to such disorder with a therapeutically-effective amount of a compound of Claim 1; or a pharmaceutically-acceptable salt or tautomer thereof.

21. A method of treating a p38 kinase mediated disorder, said method comprising treating the subject having or susceptible to such disorder with a therapeutically-effective amount of a compound of Claim 1; or a pharmaceutically-acceptable salt or tautomer thereof.

22. A method of treating inflammation, said method comprising treating the subject having or susceptible to inflammation with a therapeutically-effective amount of a compound of Claim 1; or a pharmaceutically-acceptable salt or tautomer thereof.

23. A method of treating arthritis, said method comprising treating the subject having or susceptible to arthritis with a therapeutically-effective amount of a compound of Claim 1; or a pharmaceutically-acceptable salt or tautomer thereof.

24. The method of Claim 20 wherein the p38 TNF mediated disorder is selected from the group of disorders consisting of bone resorption, graft vs. host reaction, atherosclerosis, arthritis, osteoarthritis, rheumatoid arthritis, gout, psoriasis, topical inflammatory disease state, adult respiratory distress syndrome, asthma, chronic pulmonary inflammatory disease, cardiac reperfusion injury, renal reperfusion injury, thrombus, glomerulonephritis, Crohn's disease, ulcerative colitis, inflammatory bowel disease and cachexia.

25. The method of Claim 20 wherein the TNF mediated disorder is inflammation.

26. The method of Claim 20 wherein the TNF mediated disorder is arthritis.

27. The method of Claim 20 wherein the TNF mediated disorder is asthma.

28. The method of claim 21 wherein the disorder is a p38α kinase mediated disorder.

29. The method of Claim 21 wherein the p38 kinase mediated disorder is selected from the group of diseases consisting of bone resorption, graft vs. host reaction, atherosclerosis, arthritis, osteoarthritis, rheumatoid arthritis, gout, psoriasis, topical inflammatory disease state, adult respiratory distress syndrome, asthma, chronic pulmonary inflammatory disease, cardiac reperfusion injury, renal reperfusion injury, thrombus, glomerulonephritis, Crohn's disease, ulcerative colitis, inflammatory bowel disease and cachexia.

30. The method of Claim 21 wherein the p38 kinase mediated disorder is inflammation.

31. The method of Claim 21 wherein the p38 kinase mediated disorder is arthritis.

32. The method of Claim 21 wherein the p38 kinase mediated disorder is asthma.

INTERNATIONAL SEARCH REPORT

Inte. .tional Application No
PCT/US 98/11684

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D401/04 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 124, no. 23, 1996 Columbus, Ohio, US; abstract no. 317062d, ZHENG-NIAN HUANG: "Synthesis and biological activities of 1-(substituted pyrazol-4-yl)-1,2,4-triazoles" page 1208; column 2; XP002080002 see abstract -& CHEMICAL ABSTRACTS, 13 th Chemical Substance Index, 1992-1996, Book 51, pages 546 - 550 XP002080001 see page 546, column 3, the compounds with the RN '175977-84-1!, '175977-75-0! see page 547, column 2, the compounds with the RN '175977-81-8!, '175977-72-7!,'175977-83-0!,'175977-78-3! -/--	1,2

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 October 1998	26/10/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Paisdor, B

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	see page 550, column 2, the compounds with the RN '175977-77-2!, '175977-74-9! see page 548, column 3, lines 10-13 the compound with the RN '155267-63-3! see page 548, column 2, the compound with the RN '175977-76-1! see page 549, column 2, the compounds with the RN '175977-82-9!, '175977-79-4!, '175977-80-7!, '175977-73-8! & CHIN. CHEM. LETT., vol. 5, no. 1, 1994, pages 31-34, ---	
A	WO 95 22545 A (BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.;USA) 24 August 1995 see abstract; claim 1; examples 1-8,26 ---	1-32
A	PATENT ABSTRACTS OF JAPAN vol. 96, no. 11, 29 November 1996 -& JP 08 183787 A (EISAI CO LTD), 16 July 1996 see abstract ---	1-32
A	US 5 486 534 A (LEE LEN F ET AL) 23 January 1996 see abstract; examples ---	1-32
A	US 5 559 137 A (ADAMS JERRY L ET AL) 24 September 1996 cited in the application see the whole document ---	1-32
P,X	ZHENGMING LI: "Syntheses of di-heterocyclic compounds; pyrazolylimidazoles and isoxazolylimidazoles" HETEROAT. CHEM., vol. 9, no. 3, 1998, pages 317-320, XP002080000 see pyrazole compounds of formula I with R being aminophenyl. see page 318; examples 9B,C -----	1,2

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/ 11684

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 20-32
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 20-32 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[] The additional search fees were accompanied by the applicant's protest.

[] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. onal Application No
PCT/US 98/11684

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9522545 A	24-08-1995	AT 166353 T	15-06-1998
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